ASTRO ANNUAL refresher COURSE 2021

BEST PRACTICES AND EMERGING TRENDS

March 19-21 *Live* Interactive Virtual Conference

Welcome

Tumors of the CNS
ASTRO Refresher Course
2020

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Disclosure

- Fox Chase Cancer Center employer
- I have no conflicts of interest to disclose

Learning Objectives

- Apply modern therapies/techniques to management of brain tumors
- Support decision-making with evidence
- Understand treatment controversies and individualize treatment

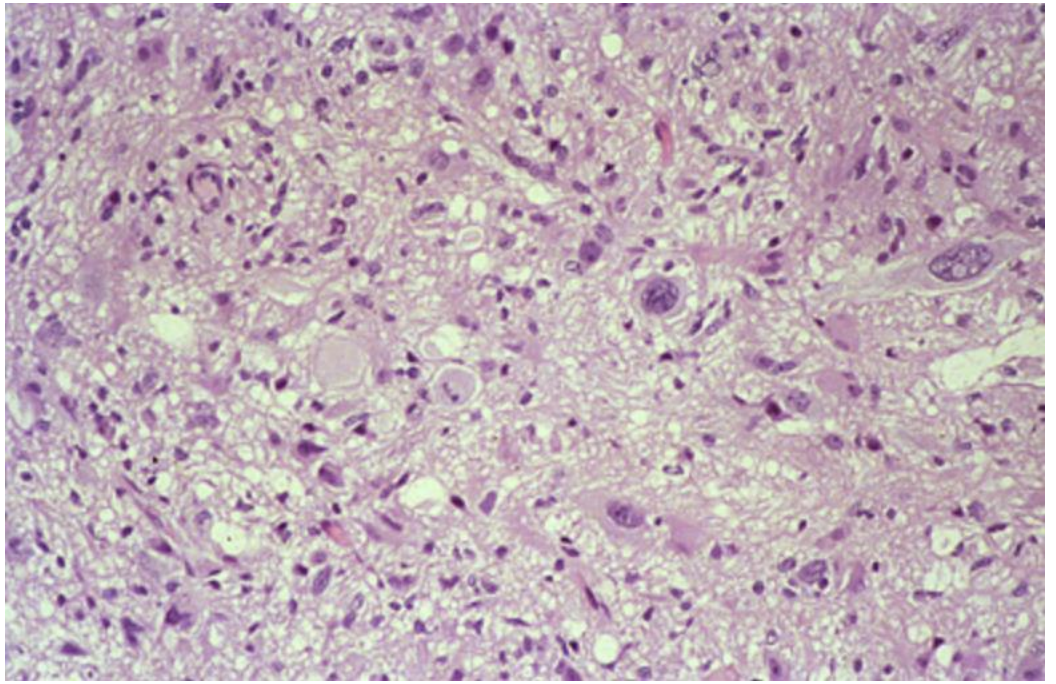
High Grade Glioma

Changes is Glioma Classification

- Old Classification: Histologic appearance
- New Classification: Histologic appearance and molecular profile.
  - Astro vs. oligo designation= “diffuse glioma”
- New classification due 2021
  - Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW)

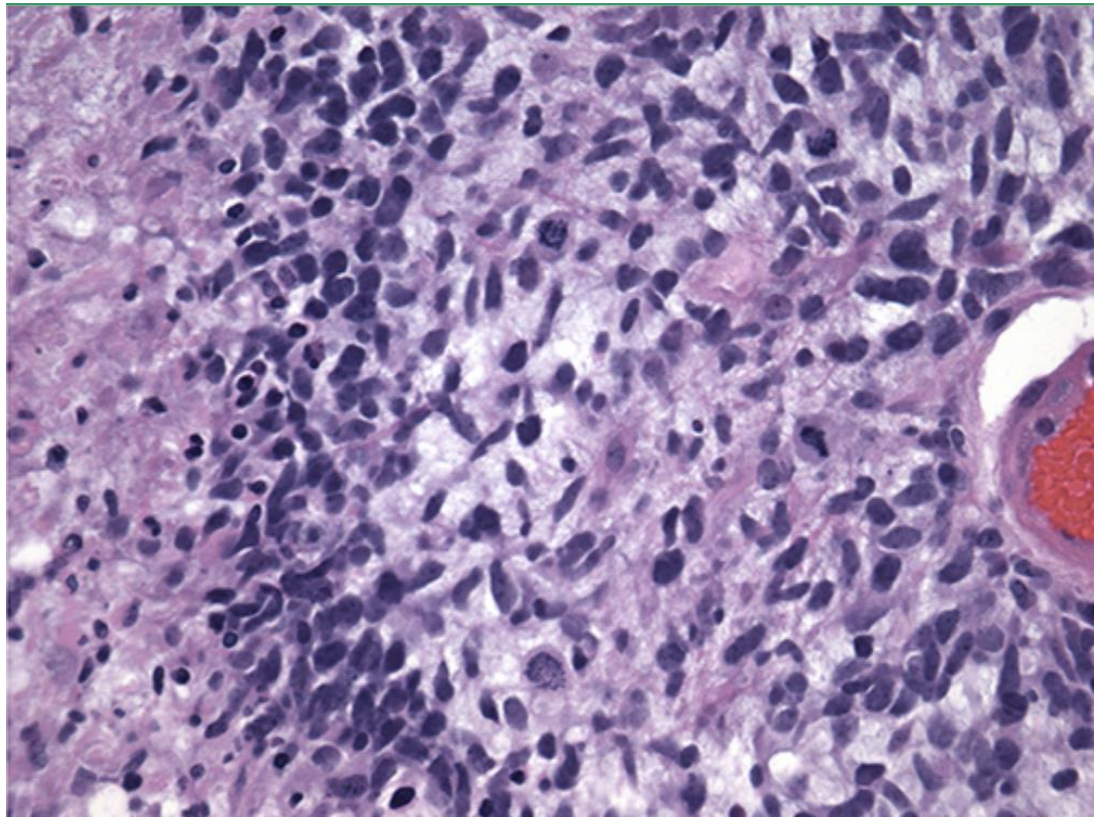
Anaplastic Glioma

- Nuclear atypia
- Increased mitotic activity
- Marked nuclear pleomorphism
- Mitotic figures
- *Lack of endothelial vascular proliferation or necrosis*

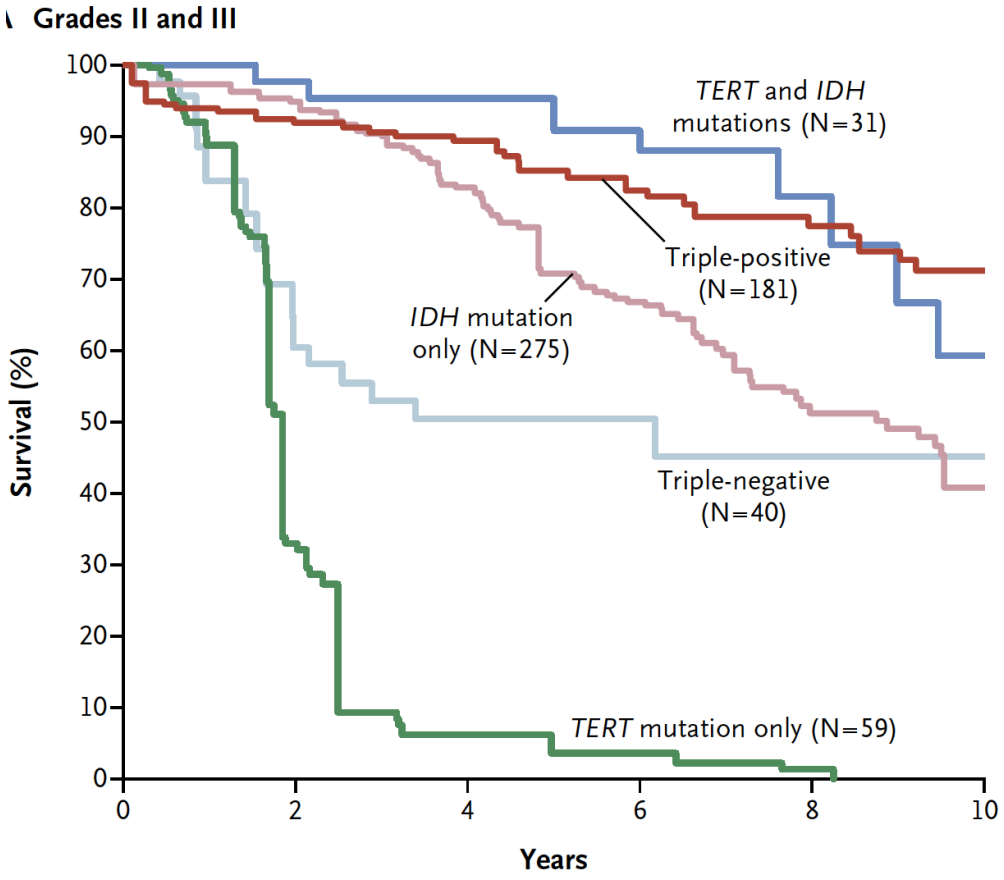


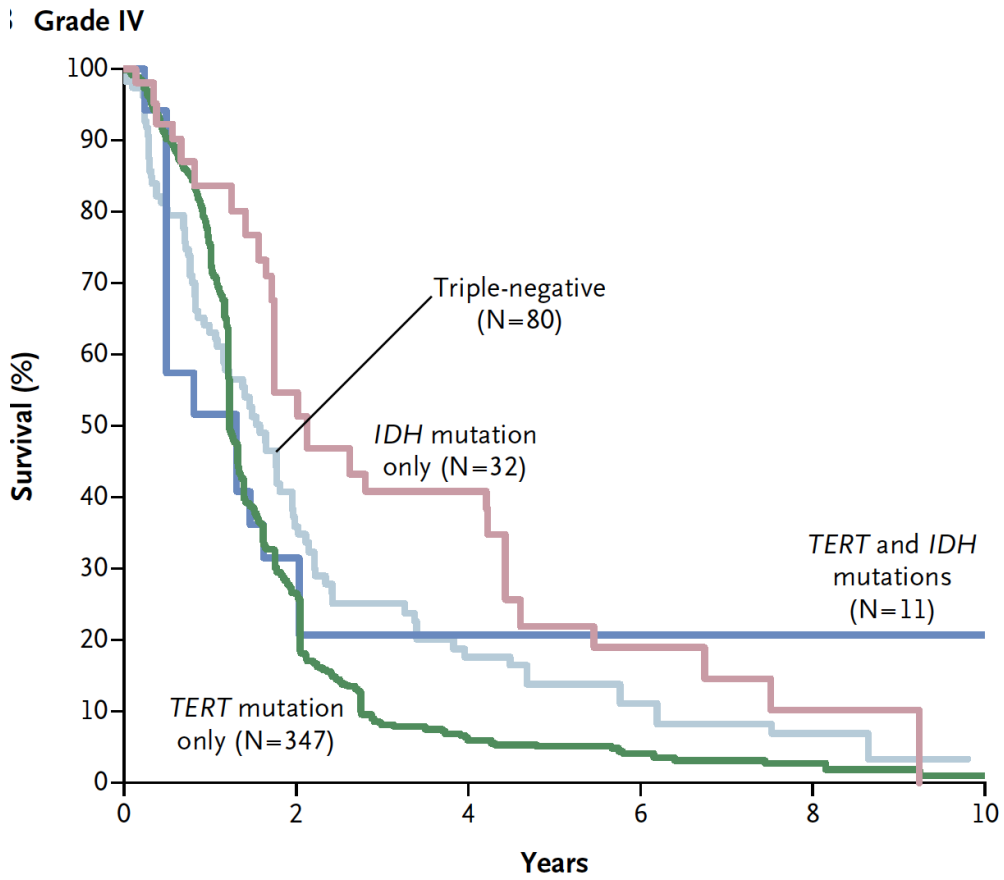
Histopathologic GBM

- Micro*vascular proliferation*
- *Necrosis* with palisading of nuclei



Prognosis by molecular profile

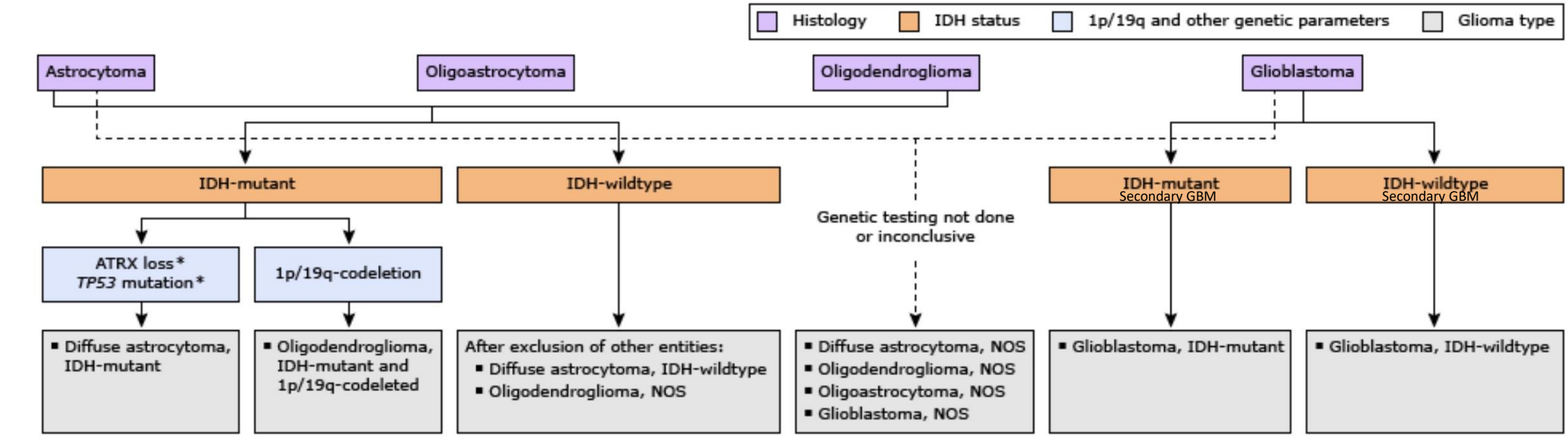




NEJM Eckel-Passow et al 372;26: 2499-2507

Integrated Diagnosis

World Health Organization (WHO) classification of diffuse gliomas



IDH: isocitrate dehydrogenase; ATRX: alpha-thalassemia/mental retardation syndrome X-linked; NOS: not otherwise specified.
* Characteristic, but not required for diagnosis.

Uptodate.com

Presentation

- Headache: 60%
- Seizure 30%
- Focal symptom: 15%

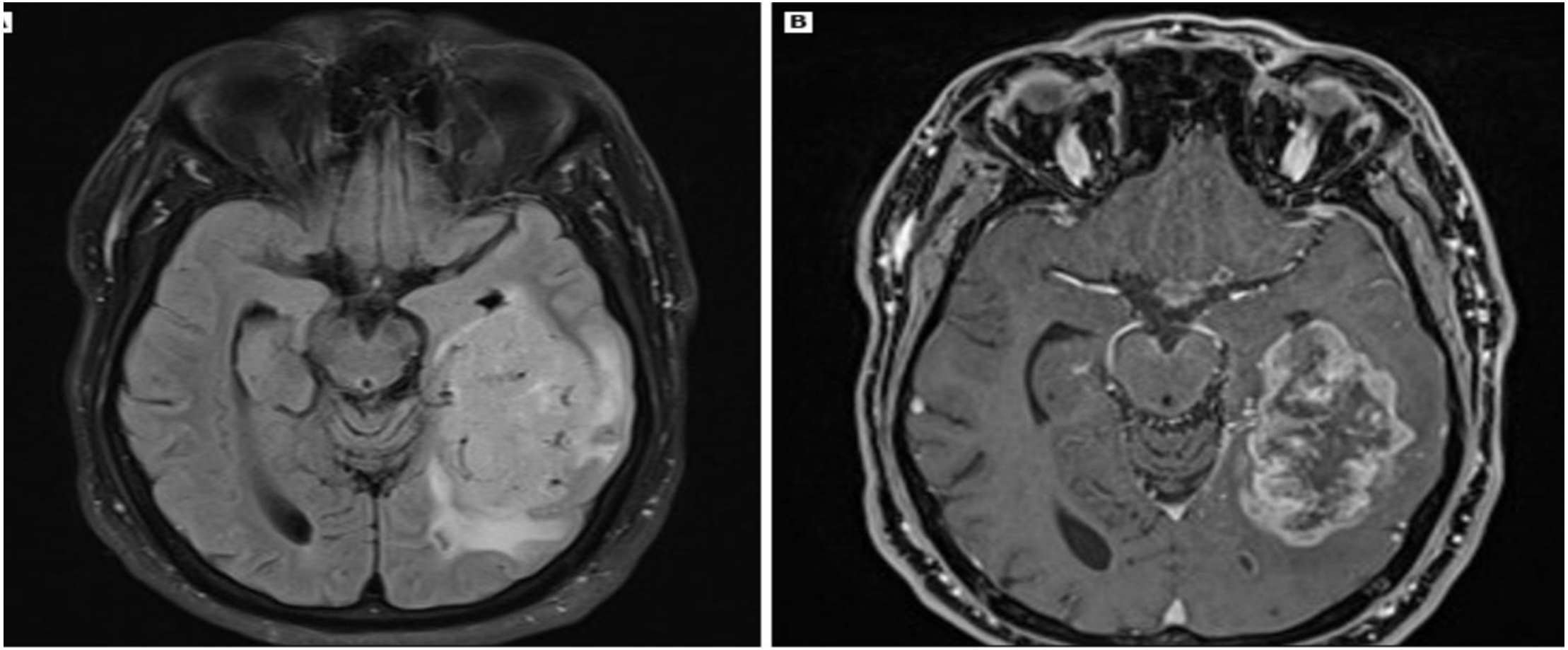
- Li-Fraumeni Syndrome
- Lynch syndrome
- Constitutional mismatch repair-deficiency

- Ionizing radiation: 5-yrs to decades

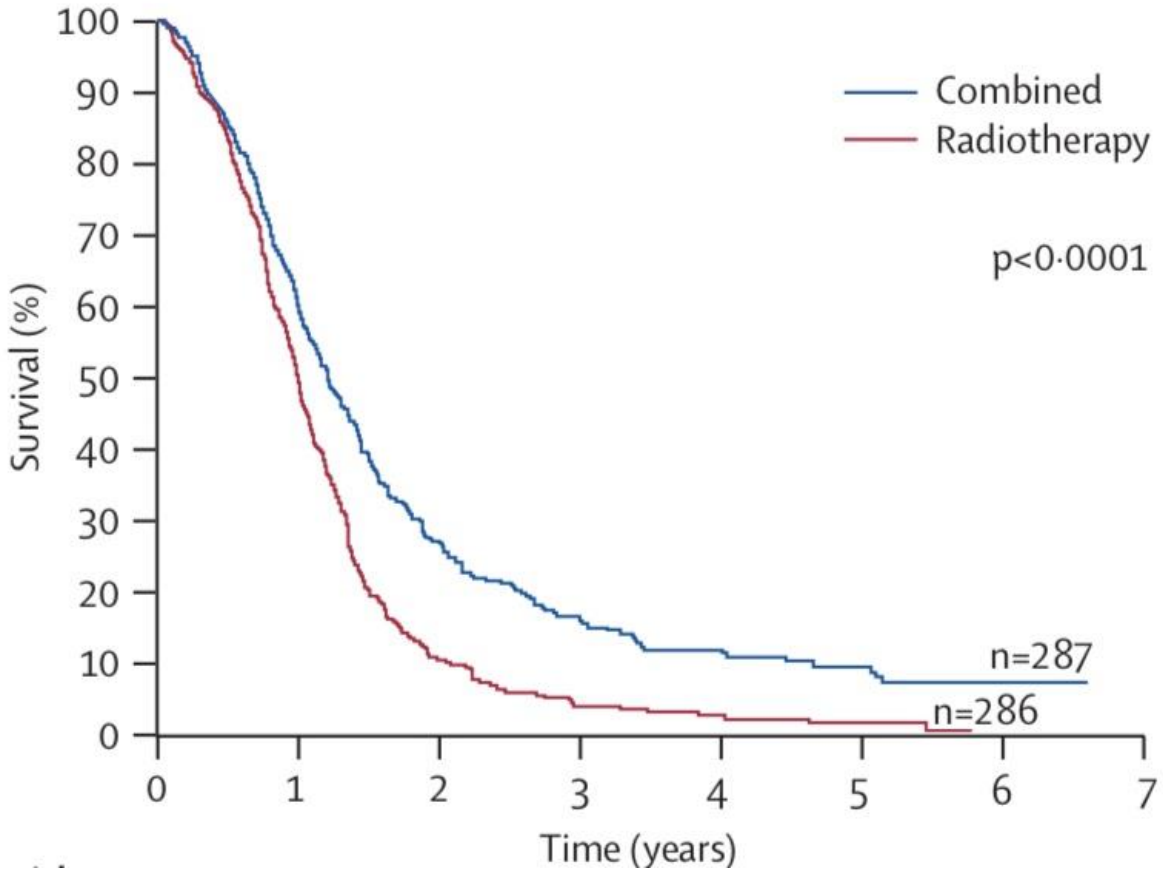
Neuro-imaging

- Enhance with contrast
- Often rim-enhancing with central necrosis
- Increased T2/Flair signal

Flair/T1+C



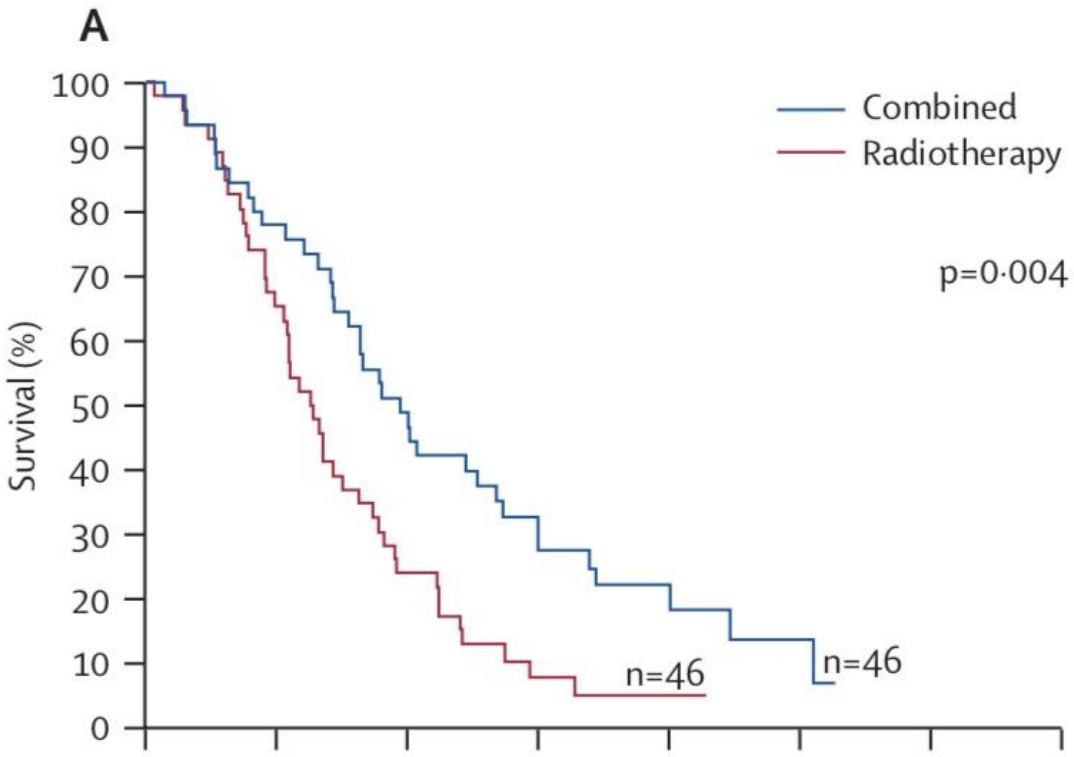
Glioblastoma



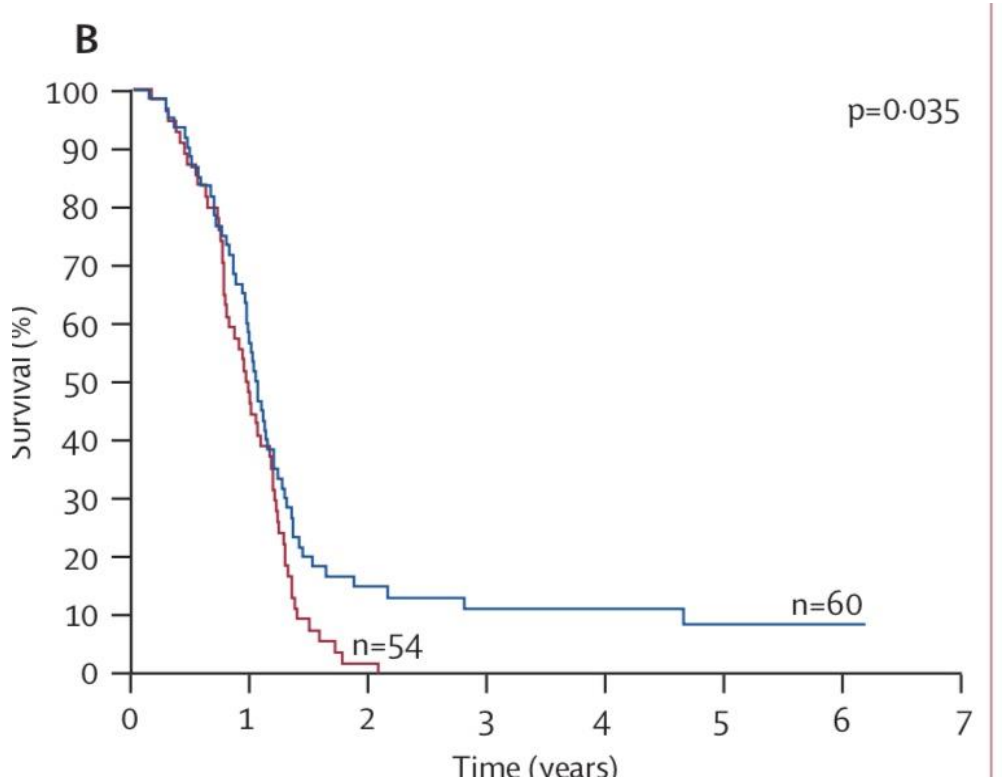
Stupp R. Lancet Oncol. 2009;10(5):459-466-7.

RT vs CRT adjusted by MGMT

Met-MGMT

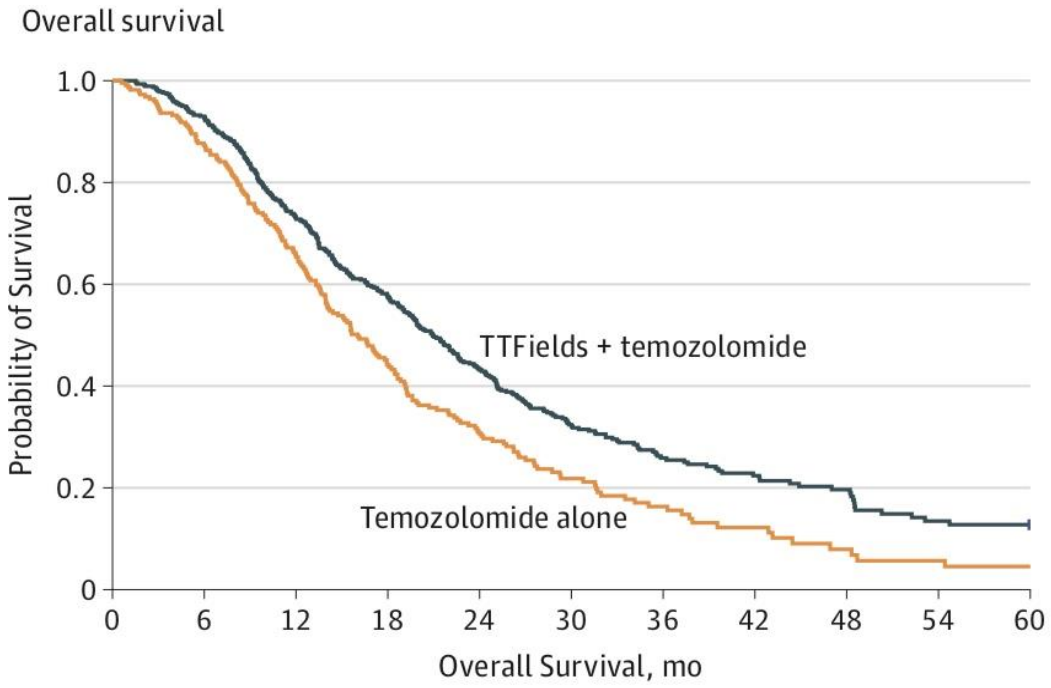


Unmet-MGMT

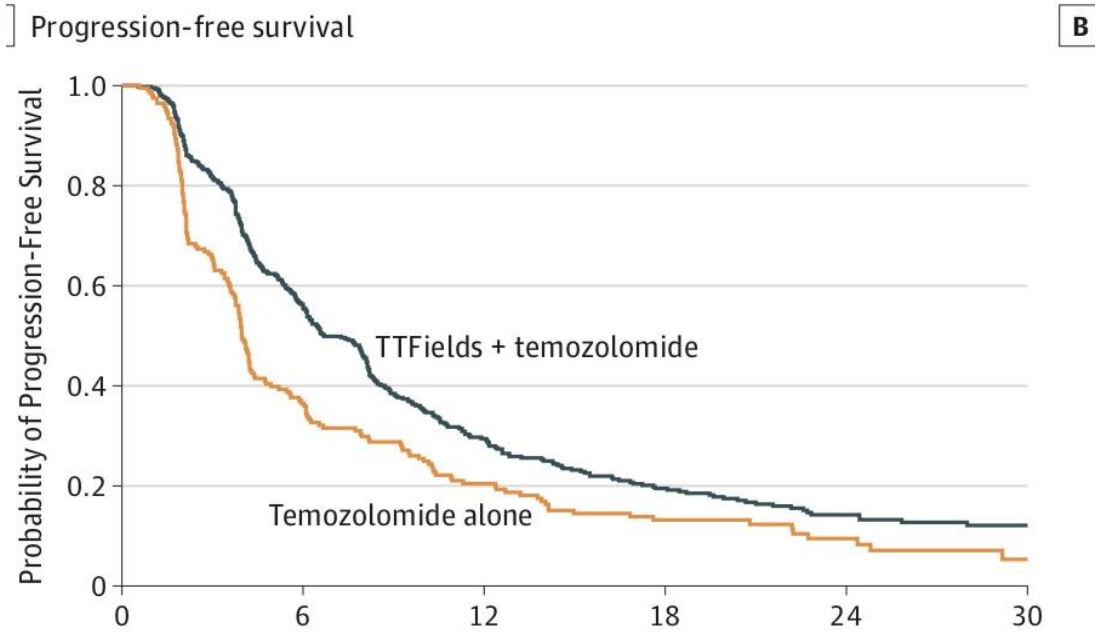


Tumor Treating Fields

OS



PSF



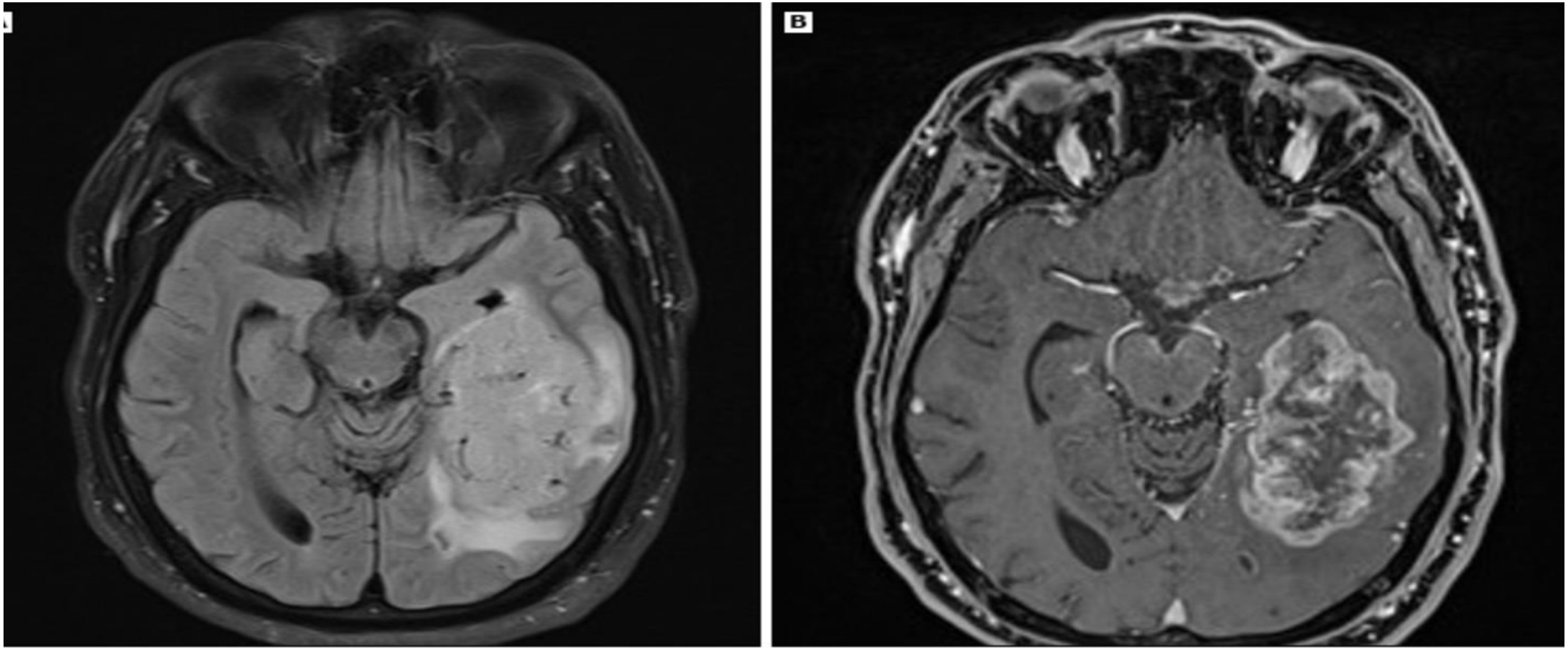
Stupp R. JAMA. 2017;318(23):2306-2311.

Treatment Planning

- Flair + 1.5 cm to CTV: 2 Gy to 46 Gy
  - add any T1+c and cavity not encompassed by flair
- CD to contrast enhancing + cavity sum 60 Gy
- Normal constraints

- Temozolomide concurrently 75 mg/m2
- Adjuvant TMZ 150-200 mg/m2 with TTF x 6 cycles

Flair/T1+C



Role of Bevacizumab

- Restricted to mass effect
- Relapse

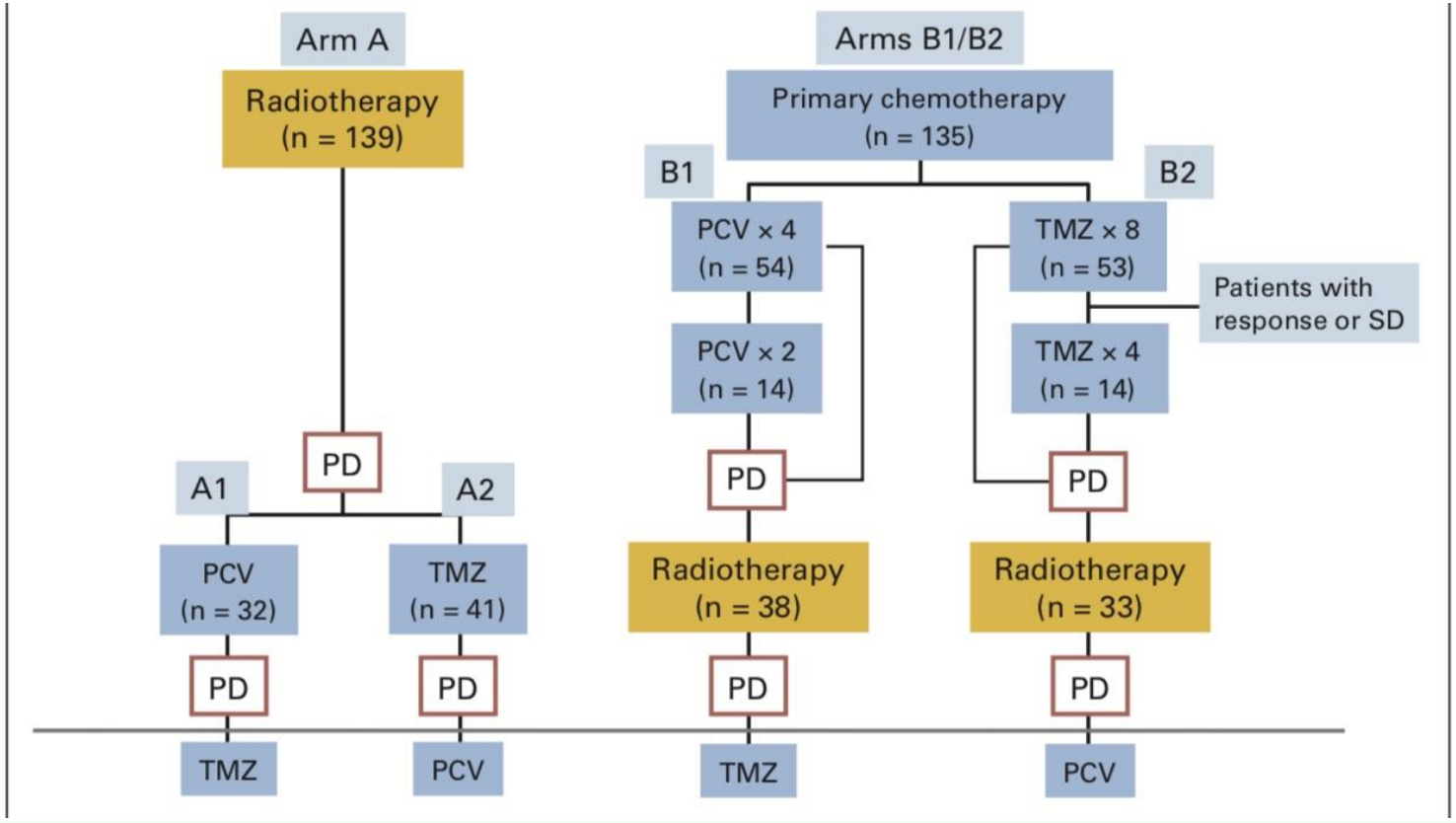
Anaplastic Gliomas

Anaplastic Gliomas

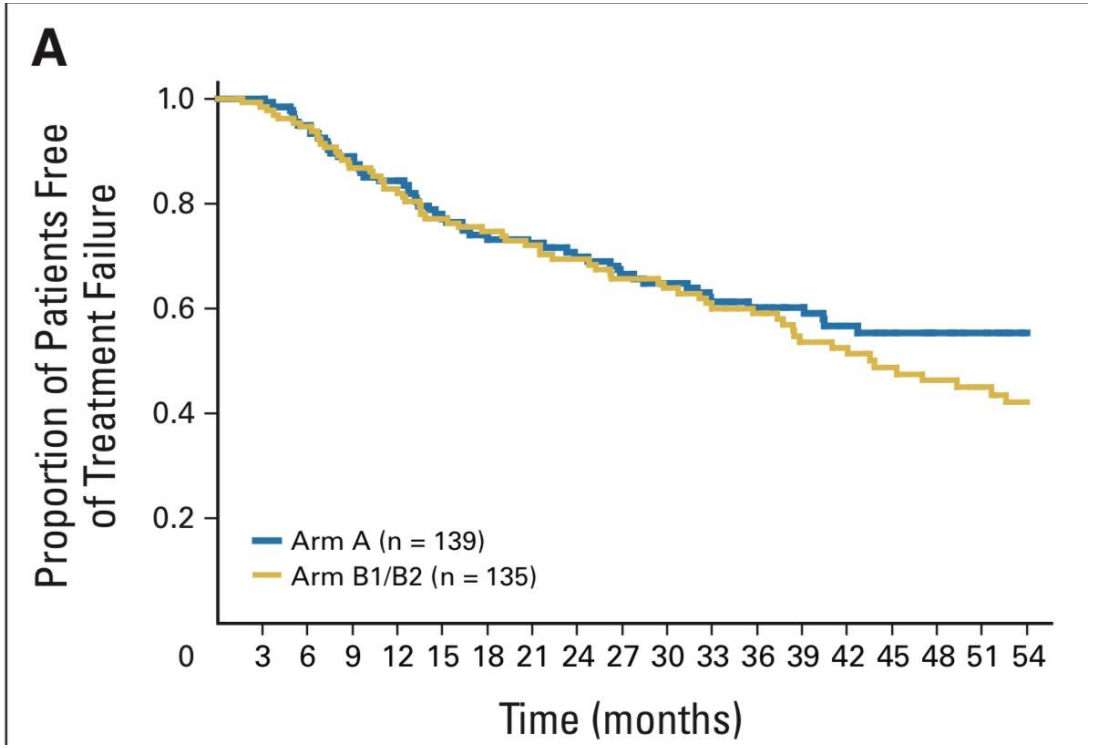
- Does de novo tx sequencing matter?

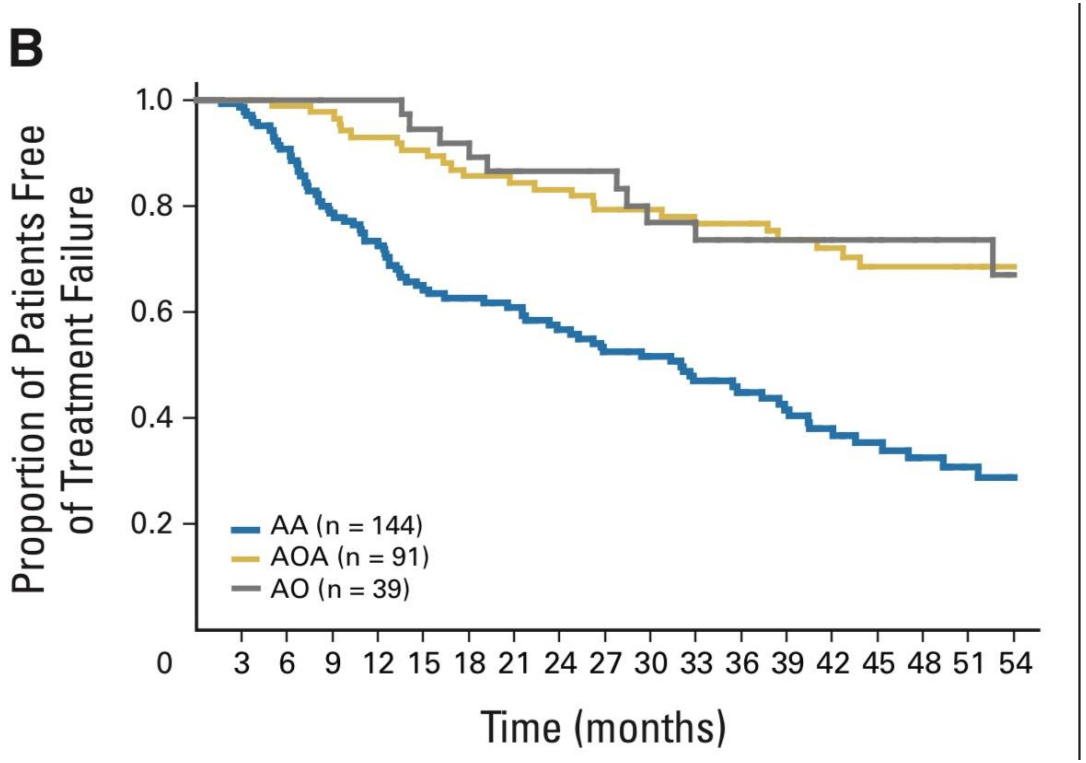
NOA-04

- *All* High-grade Glioma (AO, AA, AOA)



NOA-04


A
Proportion of Patients Free of Treatment Failure
1.0
0.8
0.6
0.4
0.2
0
3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
Time (months)
Arm A (n = 139)
Arm B1/B2 (n = 135)


B
Proportion of Patients Free of Treatment Failure
1.0
0.8
0.6
0.4
0.2
0
3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
Time (months)
AA (n = 144)
AOA (n = 91)
AO (n = 39)

Long term analysis: NOA-04

Table 6. Efficacy of arms A, B1 and B2 in CIMP^{codel}

	PCV ($n = 17$)	TMZ ($n = 16$)	Radiotherapy ($n = 35$)	P (log-rank), PCV vs TMZ
Median PFS in years (95% CI)	9.4 (3.18–n/r)	4.46 (2.01–7.8)	8.67 (6.14–11.05)	.0254
Median TTF in years (95% CI)	n/r (3.34–n/r)	5.26 (3.05–n/r)	10.12 (8.4–n/r)	.0646
Median OS in years (95% CI)	n/r (8.19–n/r)	8.09 (3.77–n/r)	n/r (9.95–n/r)	.0689

Findings held up on long term analysis however
With **codeletion, PFS: PVC > TMZ**

Wick W. Neuro-oncology. 2016;50((11)):now133-now139.

Long term analysis: NOA-04

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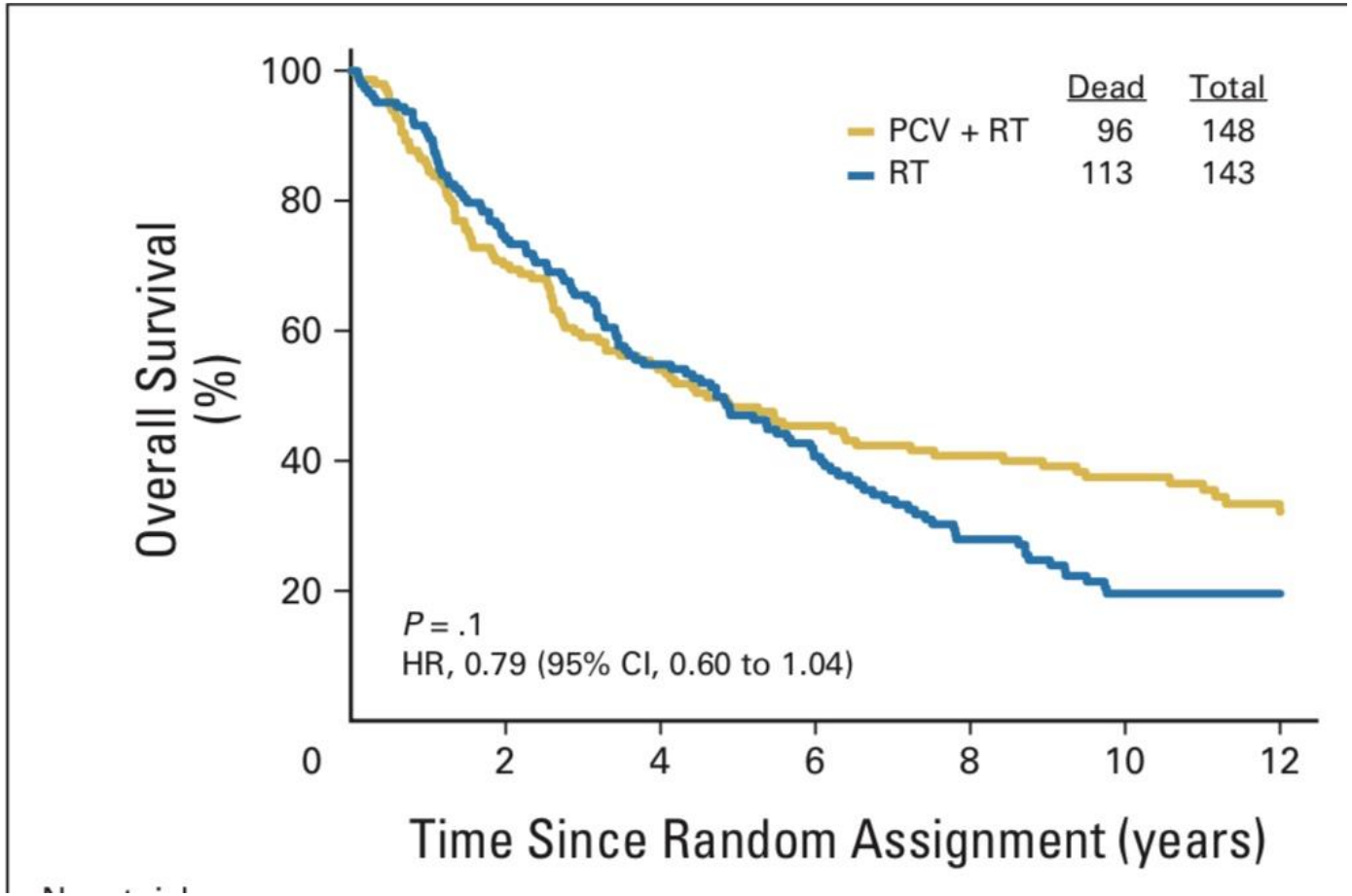
Wick W. Neuro-oncology. 2016;50((11)):now133-now139.

High Grade Oligodendroglioma

- Addition of PCV chemotherapy
  - RTOG 9402 and EORTC 26951

RTOG 9402

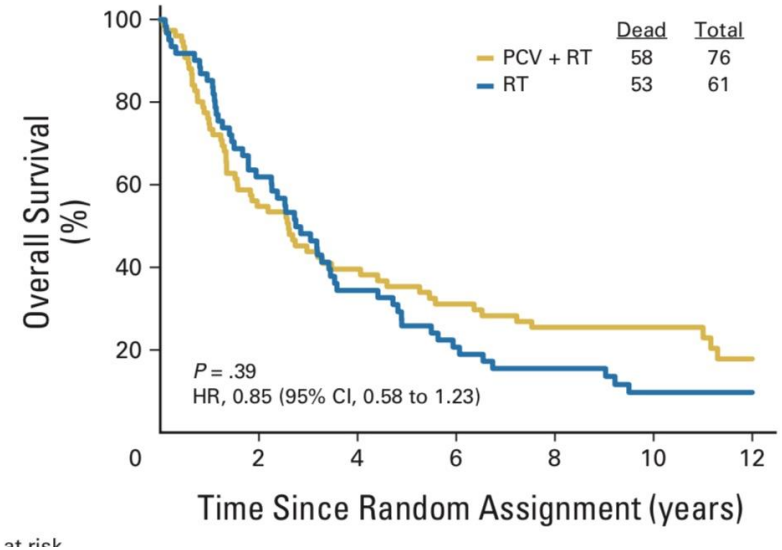


Carincross G. J Clin Oncol. 2013;31(3):337-343.

OS favored addition **of PCV adjusted for deletion**: p=0.01

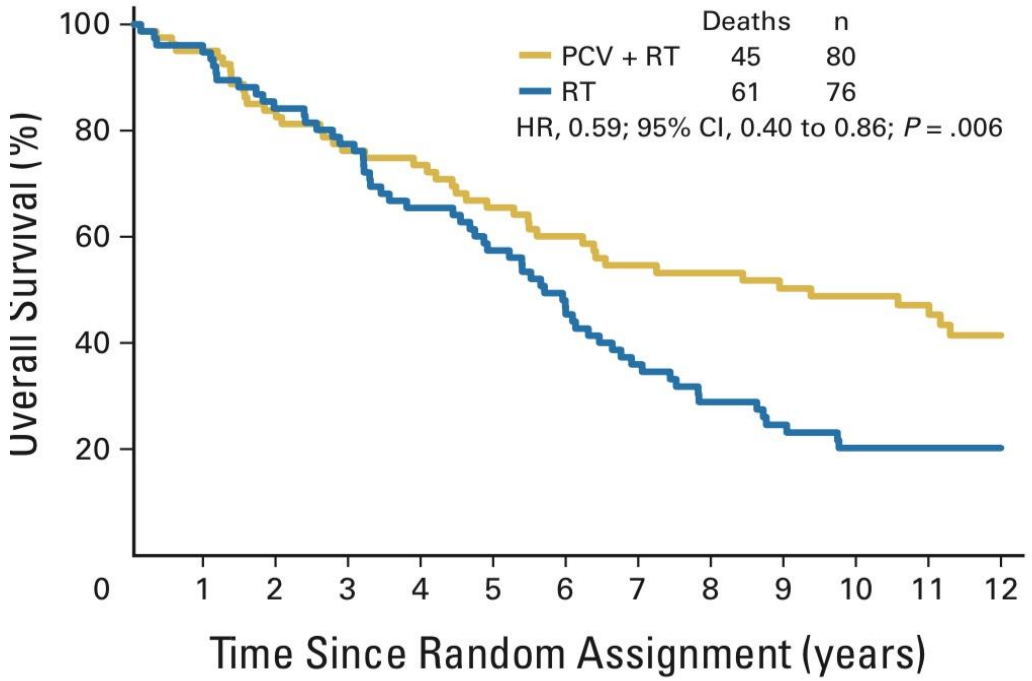
RTOG 94-02

- Some patients with non-del tumors benefited
  - Sig more patients lived ≥ 10-yrs after CRT vs RT

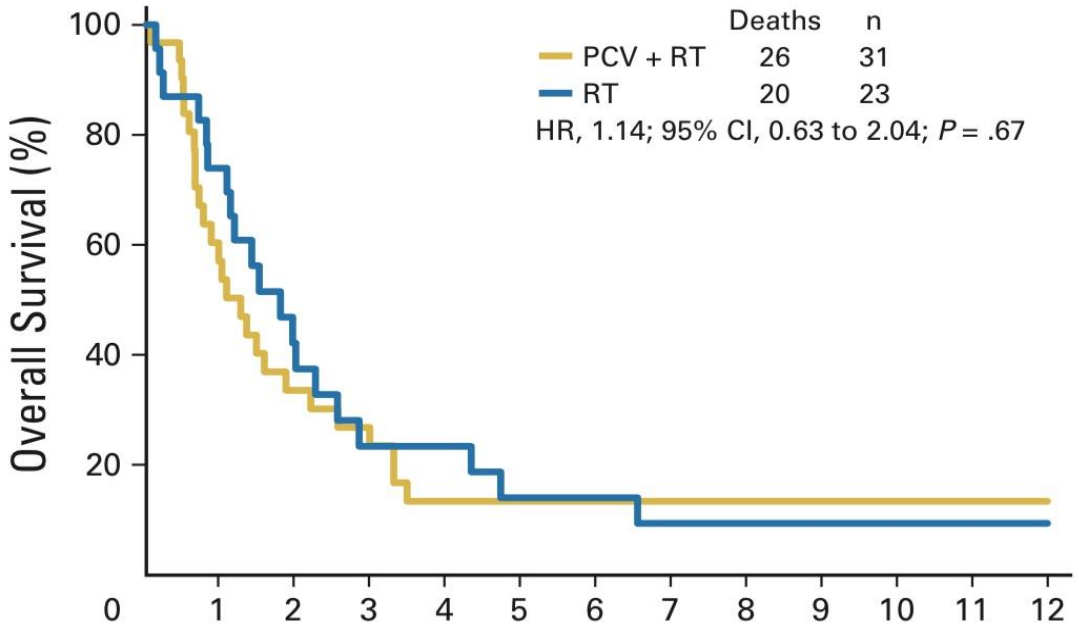


RTOG 94-02

IDH-mutated



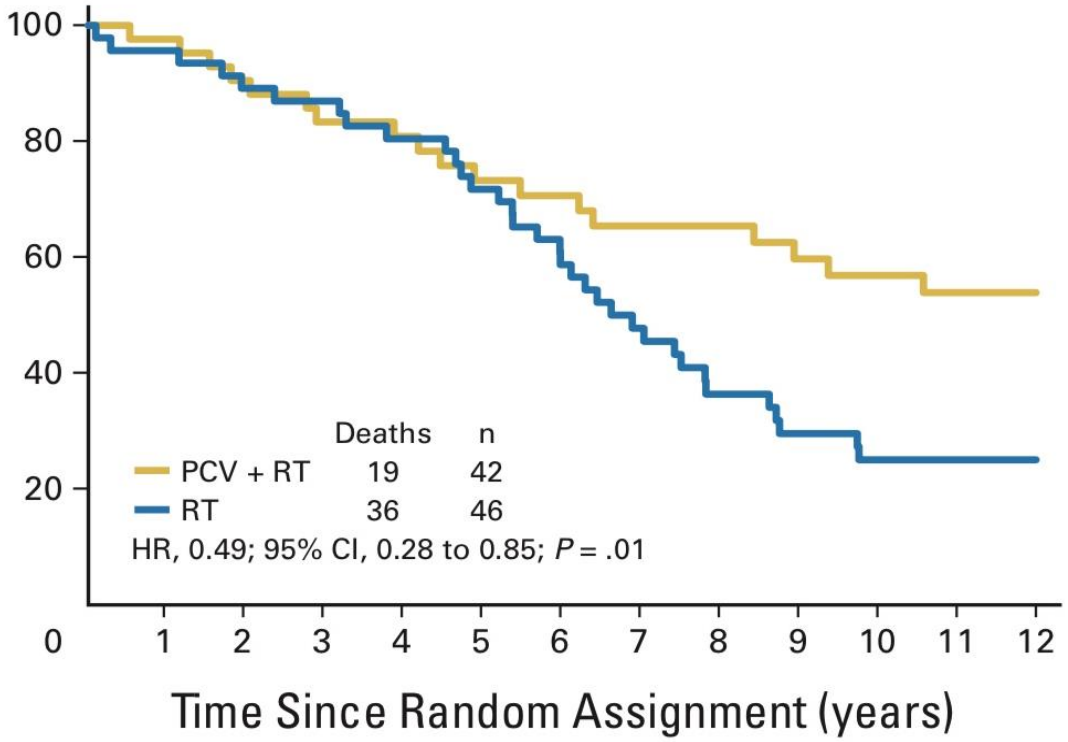
IDH-WT



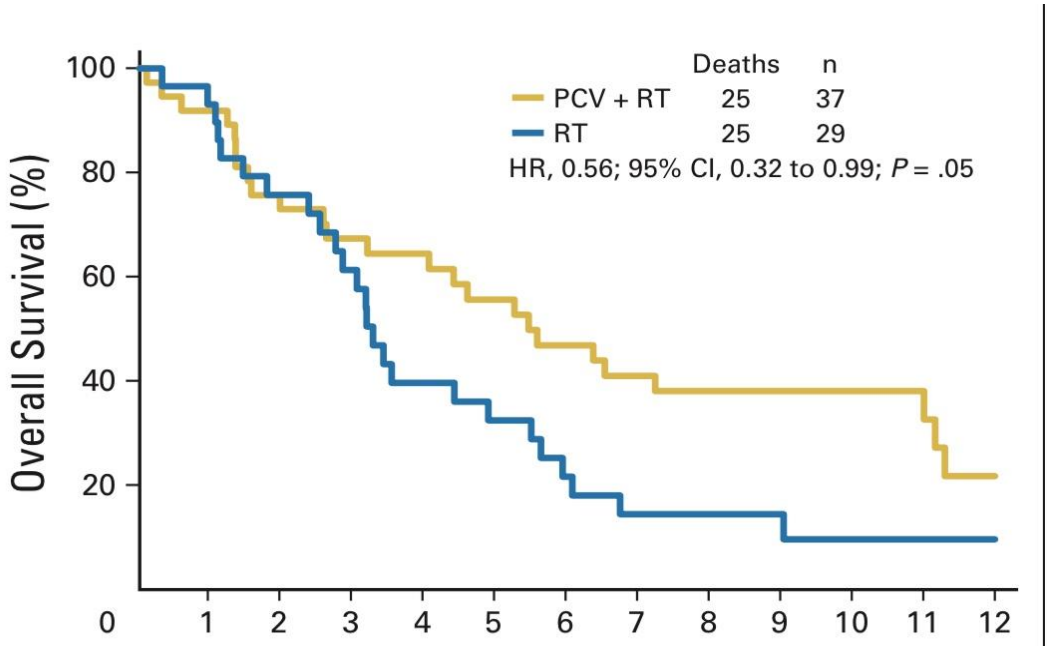
Cairncross JG,JCO. 2014;32(8):783-790.

RTOG 94-02

IDH-m + Co-del



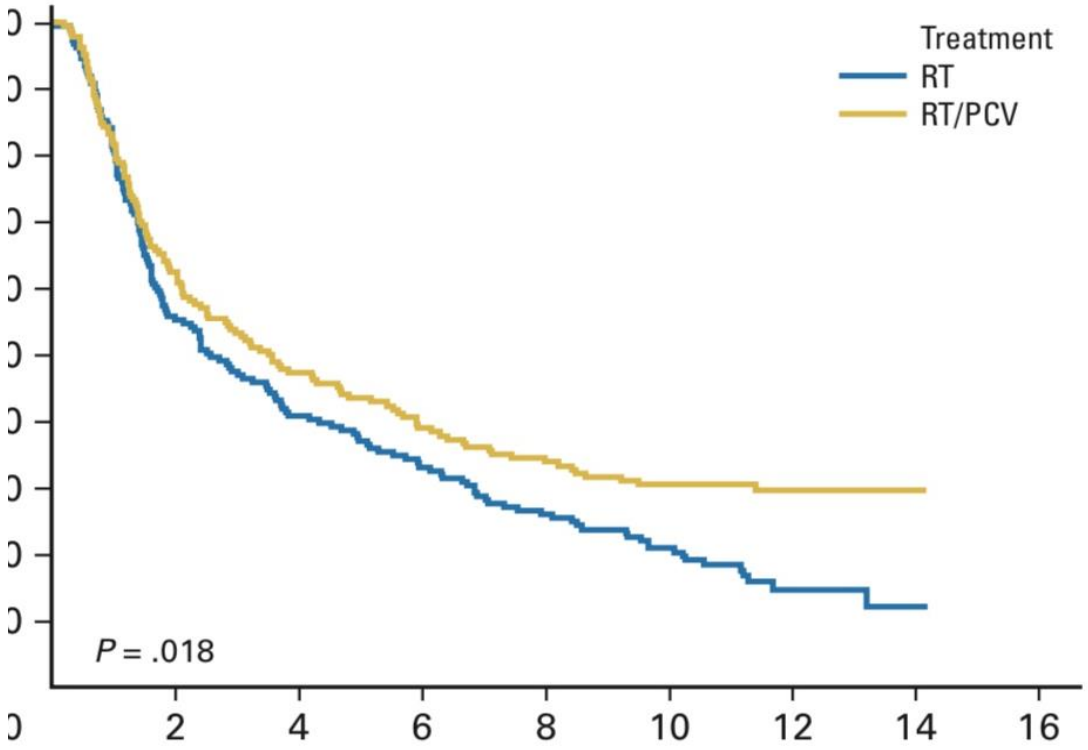
IDH-m + Non-del



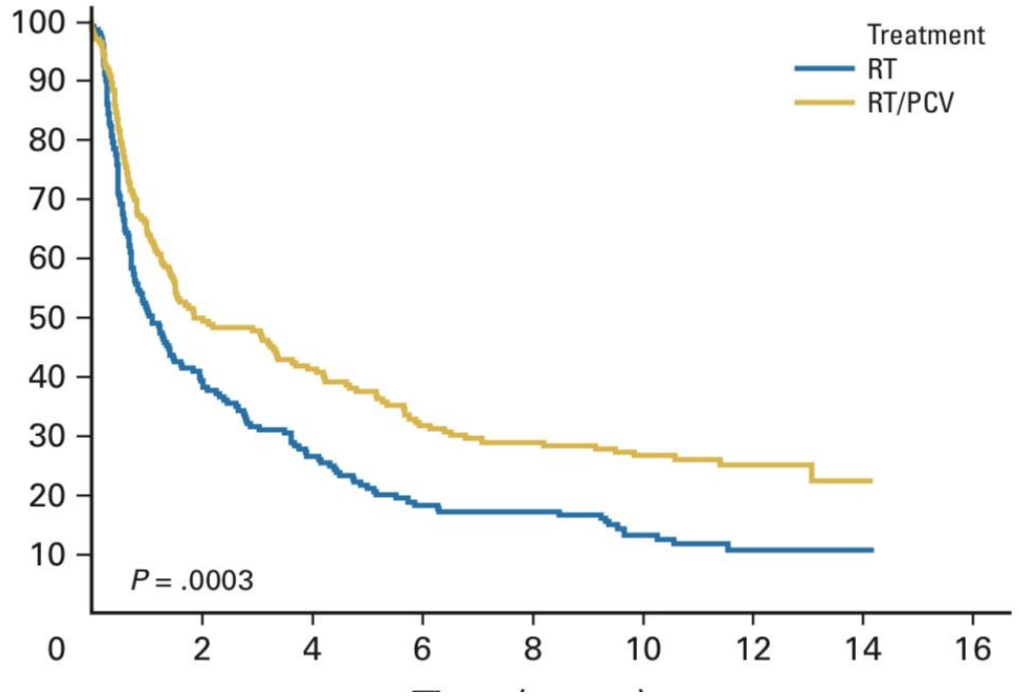
Cairncross JG,JCO. 2014;32(8):783-790.

EORTC 26951

OS

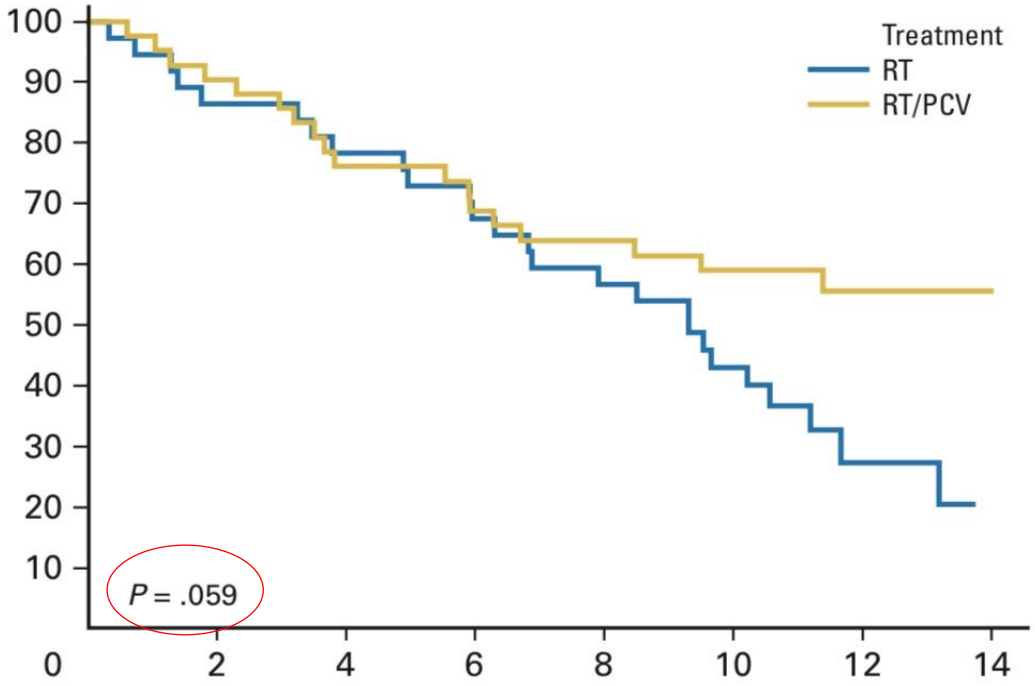


PFS

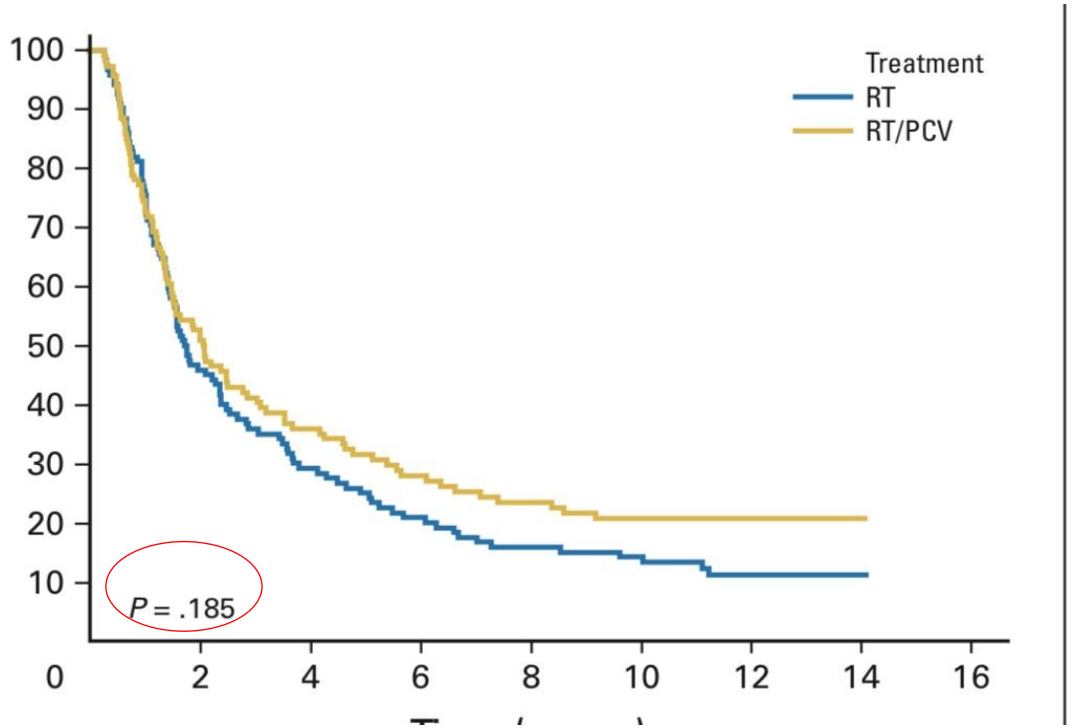


EORTC 26951

OS- Co-del

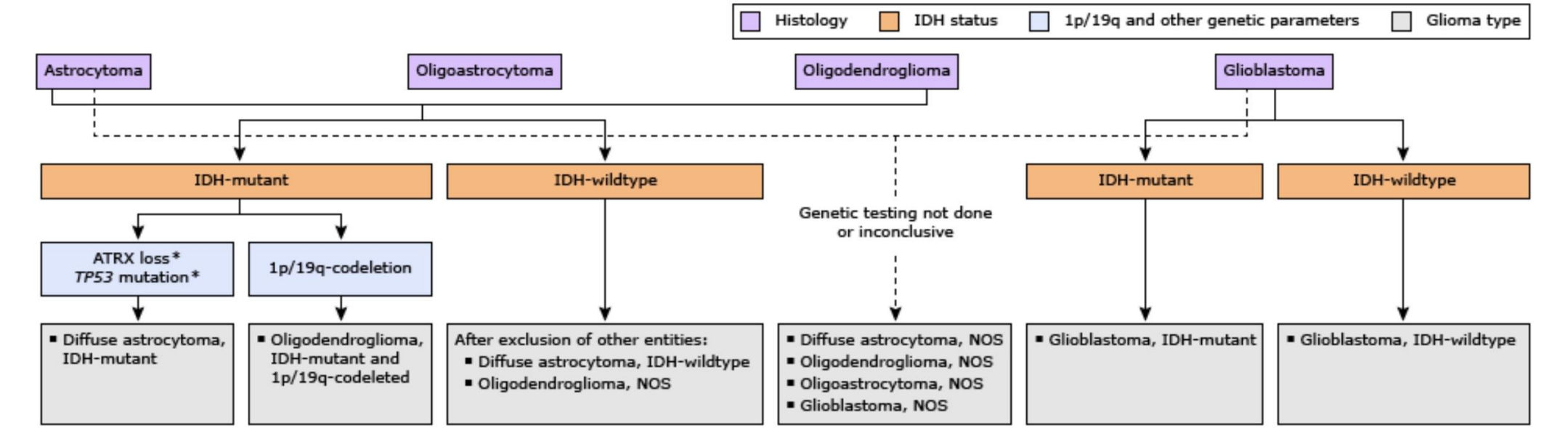


OS- Non-del



Integrated Diagnosis

World Health Organization (WHO) classification of diffuse gliomas



IDH: isocitrate dehydrogenase; ATRX: alpha-thalassemia/mental retardation syndrome X-linked; NOS: not otherwise specified.
* Characteristic, but not required for diagnosis.

Non-deleted anaplastic: CATNON

- Design
  - RT
  - Stupp regimen
  - RT+ concomitant TMZ
  - RT + adjuvant TMZ

Van den bent Lancet 2017

CATNON

	Hazard ratio (99·145% CI)	p value
Adjuvant temozolomide	0·65 (0·45–0·93)	0·0014
Age (>50 years *vs* ≤50 years)	4·04 (2·78–5·87)	<0·0001
WHO performance status score (>0 *vs* 0)	1·36 (0·94–1·96)	0·0273
1p loss of heterozygosity (yes *vs* no)	1·56 (0·84–2·88)	0·0572
Presence of oligodendroglial elements (yes *vs* no)	1·20 (0·81–1·76)	0·2230
MGMT promotor methylation before randomisation		
Methylated *vs* unmethylated	0·49 (0·26–0·93)	0·0031
Indeterminate or invalid *vs* unmethylated	0·81 (0·54–1·21)	0·1606

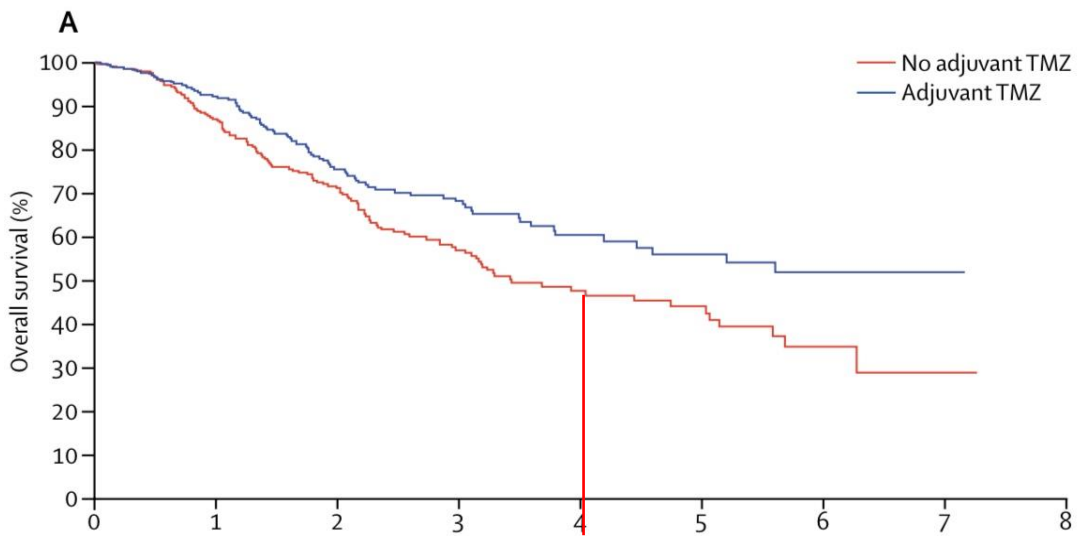
***Table 2*: Cox proportional hazards model of overall survival in patients receiving adjuvant temozolomide, adjusted by baseline stratification factors**

Amended in 2011 to include IDH

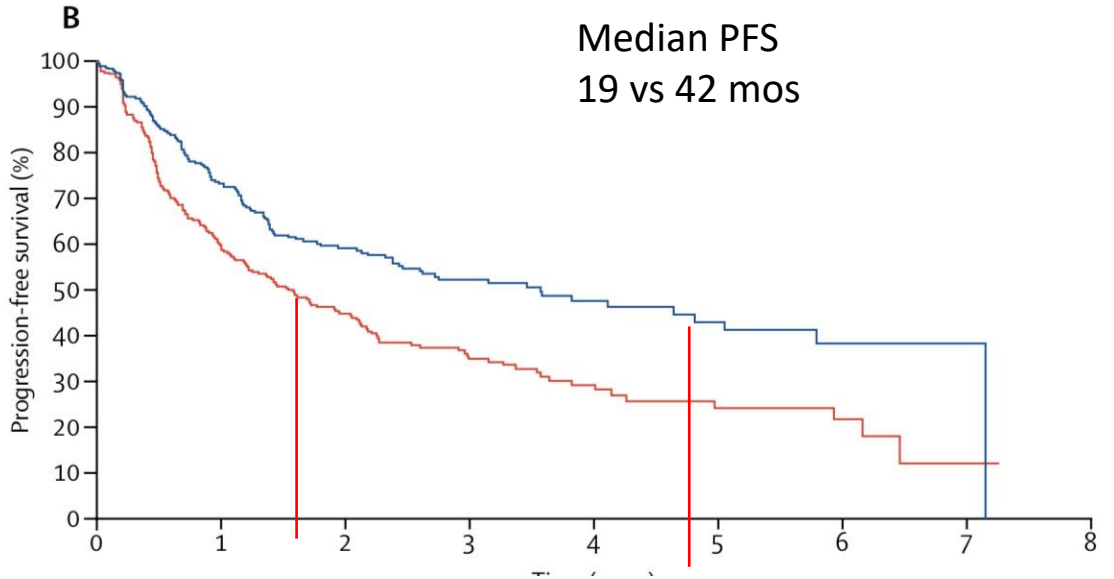
RT +/- Adjuvant TMZ

OS

P=0.0014



PFS



Median PFS
19 vs 42 mos

Outcome by IDH- ASCO update

- OS by IDH
  - mutated 116-mos vs. wt 19-mos
- mIDH+ adj TMZ (HR: 0.41, p=0.001)
- No TMZ benefit for WT-IDH

JCO 2019- ASCO

RT + cTMZ

- cTMZ HR 0.968
  - 5-yr OS: 50.2 vs. 52.7
- OS with cTMZ HR: 0.71 (ns)

JCO 2019- ASCO

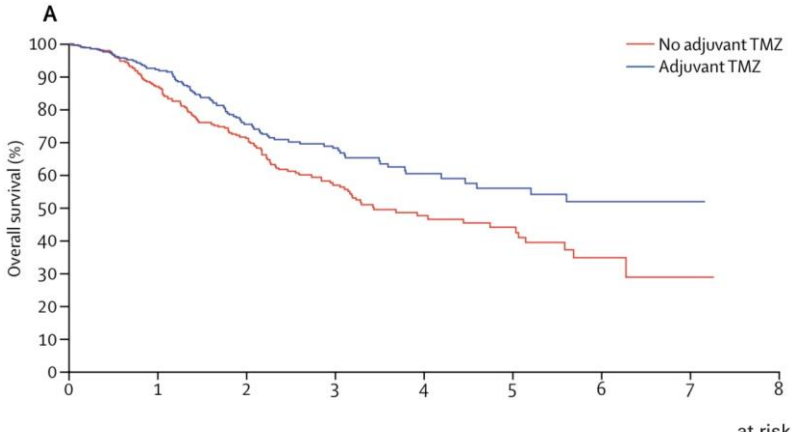
CATNON

- **Non sig trend cTMZ for mIDH**
- **AdjTMZ benefit for mIDH, not wtIDH**
- Generally recommend RT + TMZ
- Evolving

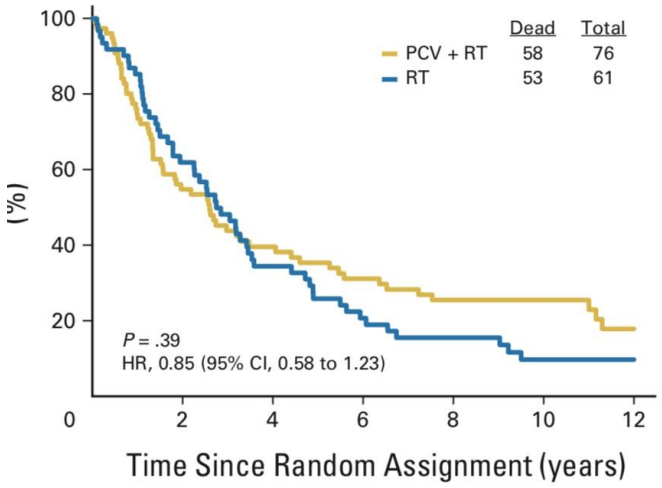
JCO 2019- ASCO

TMZ or PCV for Non-deleted

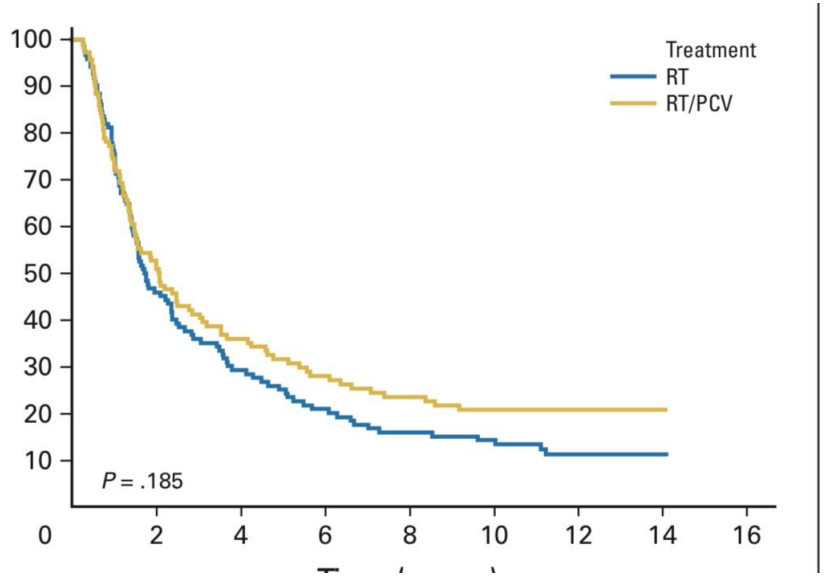
- CATNON: TMZ improves survival
- EORTC/RTOG: PCV minimal with non-deleted



CATNON



RTOG



EORTC

Non-deleted chemotherapy

- TMZ for non-deleted HGG

Co-deleted tumors

- Sensitivity to chemo
- Can RT be delayed for these chemo-sensitive tumors?

Codel Trial
(Alliance-N0577; EORTC 26081/22086; NRG 1071; NCIC-CEC-2)

- RT (A) vs. Stupp (B) vs. TMZ (C)
- OS primary end point

- PFS C vs. A+B

Jaeckle K. CODEL; Neurology. 2016;April 05, 2016; 86 (16 Supplment)

Outcomes

- PFS
  - TMZ: 2.5 years
  - RT: Not reached (p=0.001)
- Dead from Disease
  - TMZ: 33%
  - RT: 4% (p=0.03)
- Risk of Death
  - TMZ: HR=9.2 (p=0.048)

Codel

- Closure of TMZ only arm
- Arm A: Δ to RT+PCV based on RTOG/EORTC

High-Grade Glioma in Elderly

Treatment versus supportive care in GBM

- Randomized 85 patients at 10 centers
- RT vs. Supportive care
- Discontinued at first interim analysis
- OS 29 vs 17 weeks (p=0.002)
- No severe adverse events
- QOL and cognitive evaluations not different

Keime-Guibert et al. N Engl J Med. 2007;356(15):1527-1535.

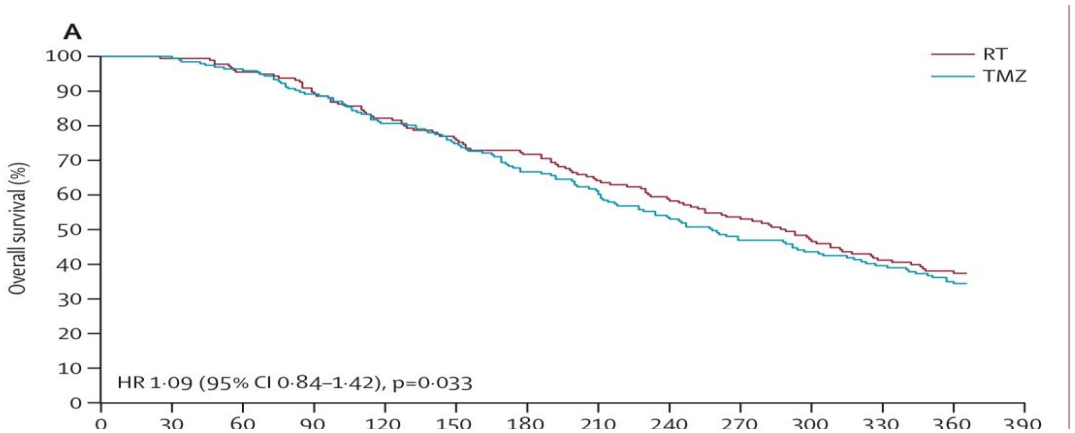
TMZ vs RT High-Grade Astrocytoma NOA-08

- >65-yrs.
- Endpoint OS
- Non-inferiority of chemo with 25% margin

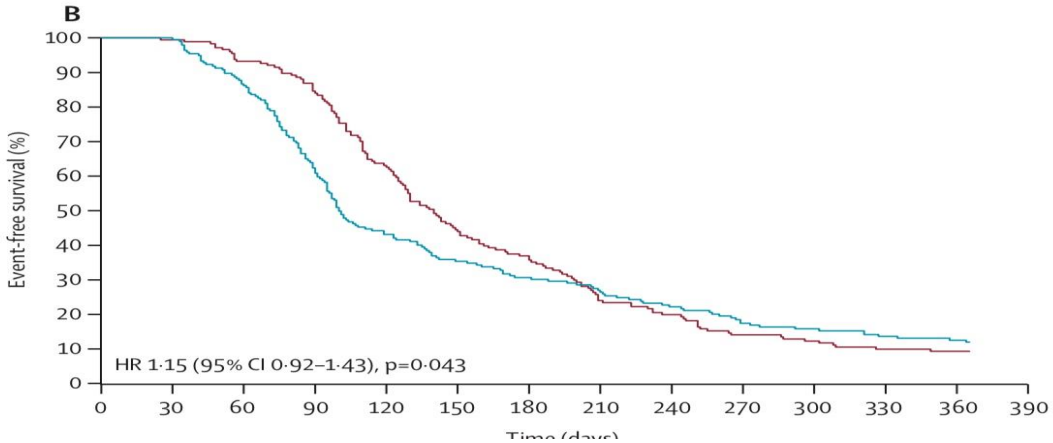
Wick et al. Lancet 2012; 13(7):707-15.

NOA-08

Overall Survival



Event-Free survival



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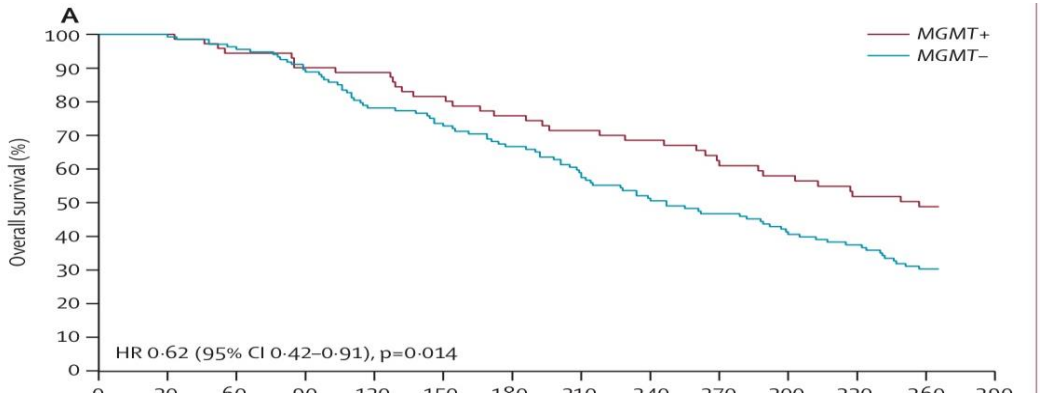
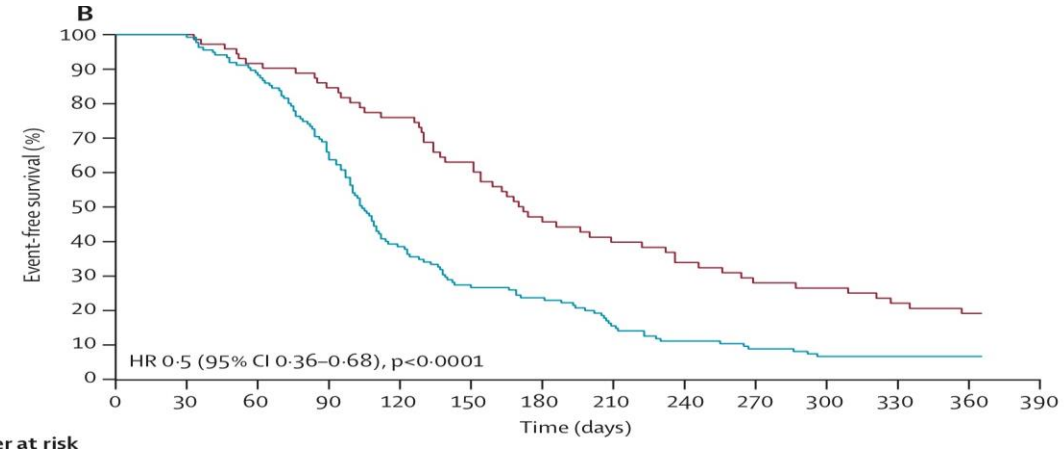
NOA-08

Overall Survival by MGMT



Event Free Survival by MGMT



ber at risk

Wick et al. Lancet 2012; 13(7):707-15.

NOA-08

- Predictive Factors

Age (years)	1·01 (0·98–1·04)	0·674
Resection		
Complete resection *vs* incomplete resection *vs* biopsy*	1·29 (1·07–1·56)	0·008
Anaplastic astrocytoma *vs* glioblastoma	0·75 (0·45–1·24)	0·255
MGMT promoter methylation†		
Temozolomide group, methylated	0·53 (0·33–0·86)	0·01
Radiotherapy group, methylated and unmethylated	1·0‡	..
Temozolomide group, unmethylated	1·95 (1·41–2·69)	0·01

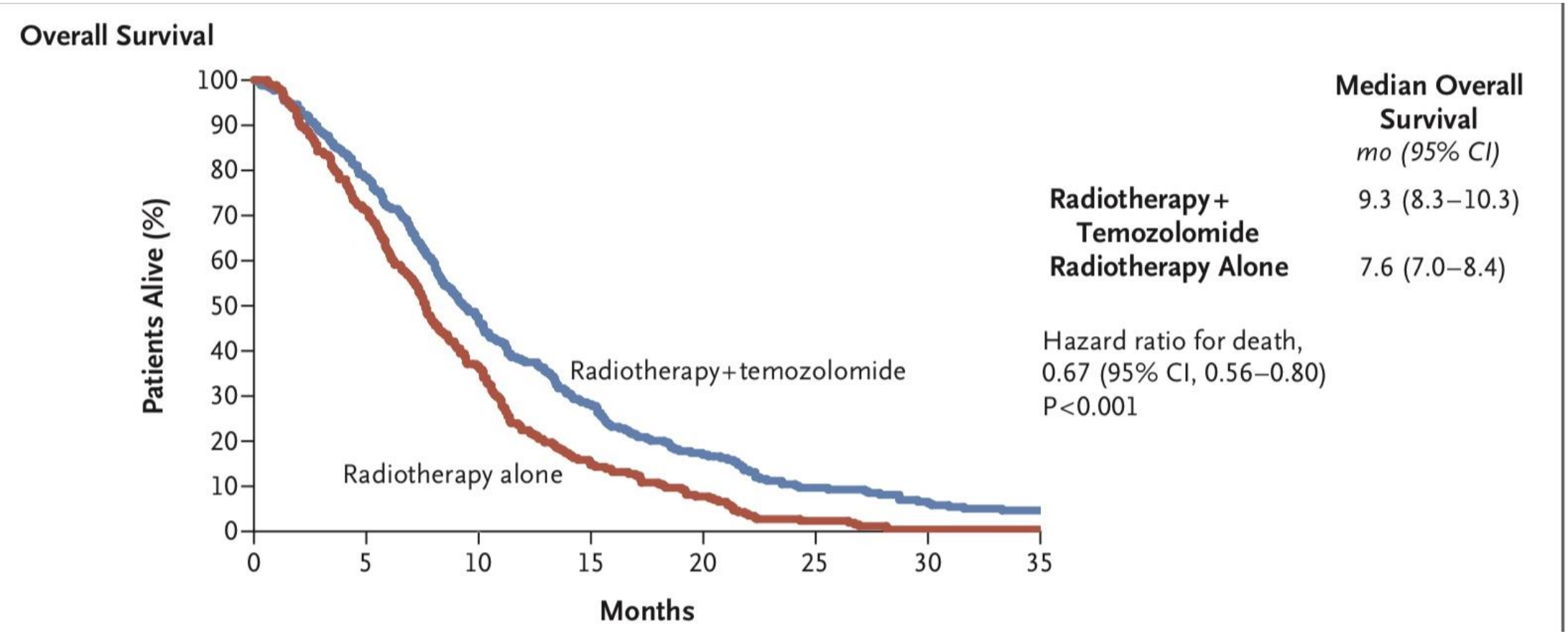
Wick et al. Lancet 2012; 13(7):707-15.

HFRT +/- TMZ

- > 65-yrs
- 40 Gy/15 fractions +/- Stupp regimen TMZ
- Exploratory analysis by MGMT

Perry JR, Laperriere N, O'Callaghan CJ, N Engl J Med. 2017;376(11):1027-1037.

hRT +/- TMZ

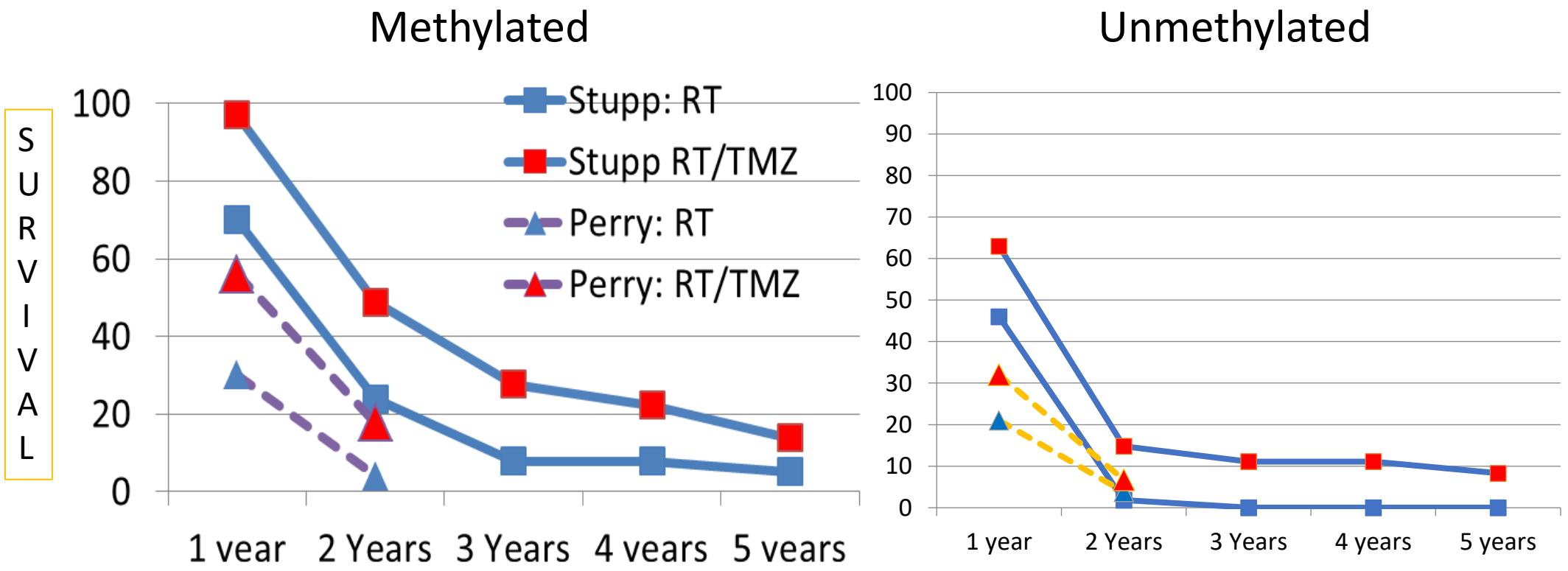

Overall Survival
Patients Alive (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Months
Radiotherapy+temozolomide
Radiotherapy alone
Median Overall Survival
mo (95% CI)
Radiotherapy + Temozolomide 9.3 (8.3–10.3)
Radiotherapy Alone 7.6 (7.0–8.4)
Hazard ratio for death, 0.67 (95% CI, 0.56–0.80)
P<0.001

Hypofx + TMZ

- mMGMT predictive when TMZ added to RT
- Clinical benefit of TMZ in uMGMT observed, did not meet significance.
- ≤ 70-yrs benefited less
- *No direct comparison to Stupp*

Survival *across studies* by MGMT status

Stupp, age <70 and Perry, age >65



From ACRO 2018 talk by Stuart “Skip” Grossman

Progression: RANO Criteria

- < 12 weeks
- New enhancement outside 80% IDL only considered progressive

- =/> 12 weeks
- Increase T2/flair on antiangiogenic therapy
- Even if no change in enhancement (pseudoresponce)

Wen et al JCO 28(11) 2010

Low(er) Grade Glioma

Epidemiology

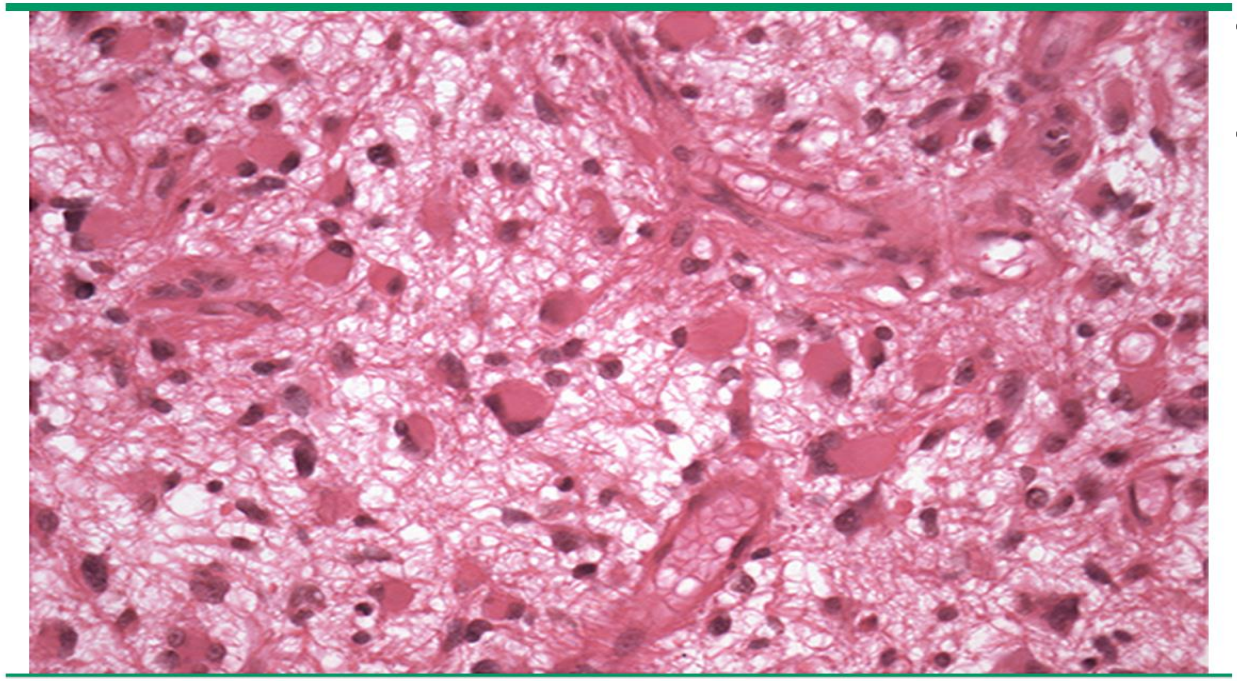
- ~2000 LGG diagnosed in US/yr
- 15% of all primaries
- Seizure in up to 80%
  - “favorable” prognostic factor compared to abnormal exam, other neurologic deficits

Heterogeneous group

Pathology	OS
Diffuse astrocytomas	5 years
Oligoastrocytomas	7.5 years
Oligodendroglioma	10 years

Astrocytoma

Diffuse astrocytoma



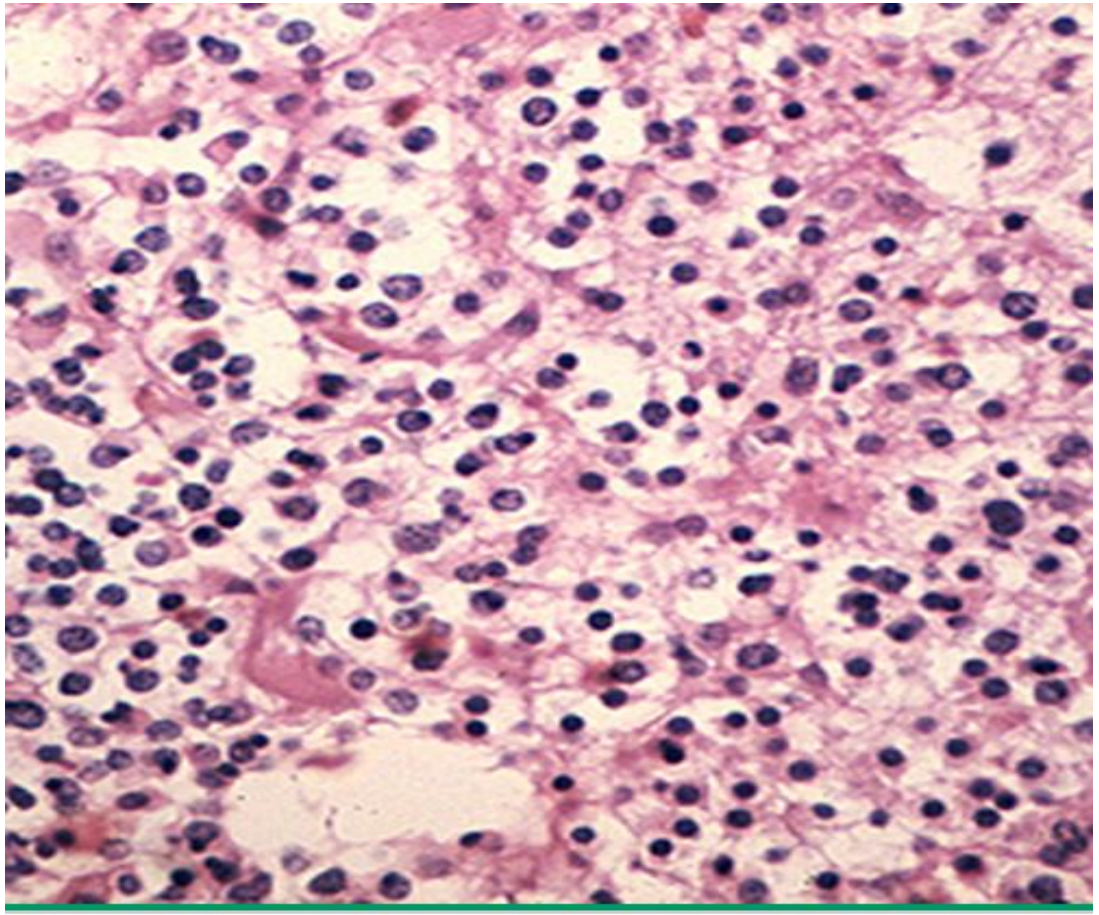
Histological features include the prominent eosinophilic cytoplasm in some astrocytic tumor cells (gemistocytes) as well as the fibrillary background.

Courtesy of Dr. David Louis.

- Neuro-glial fibrils
- *GFAP* positive.

Uptodate.com

Oligodendroglioma



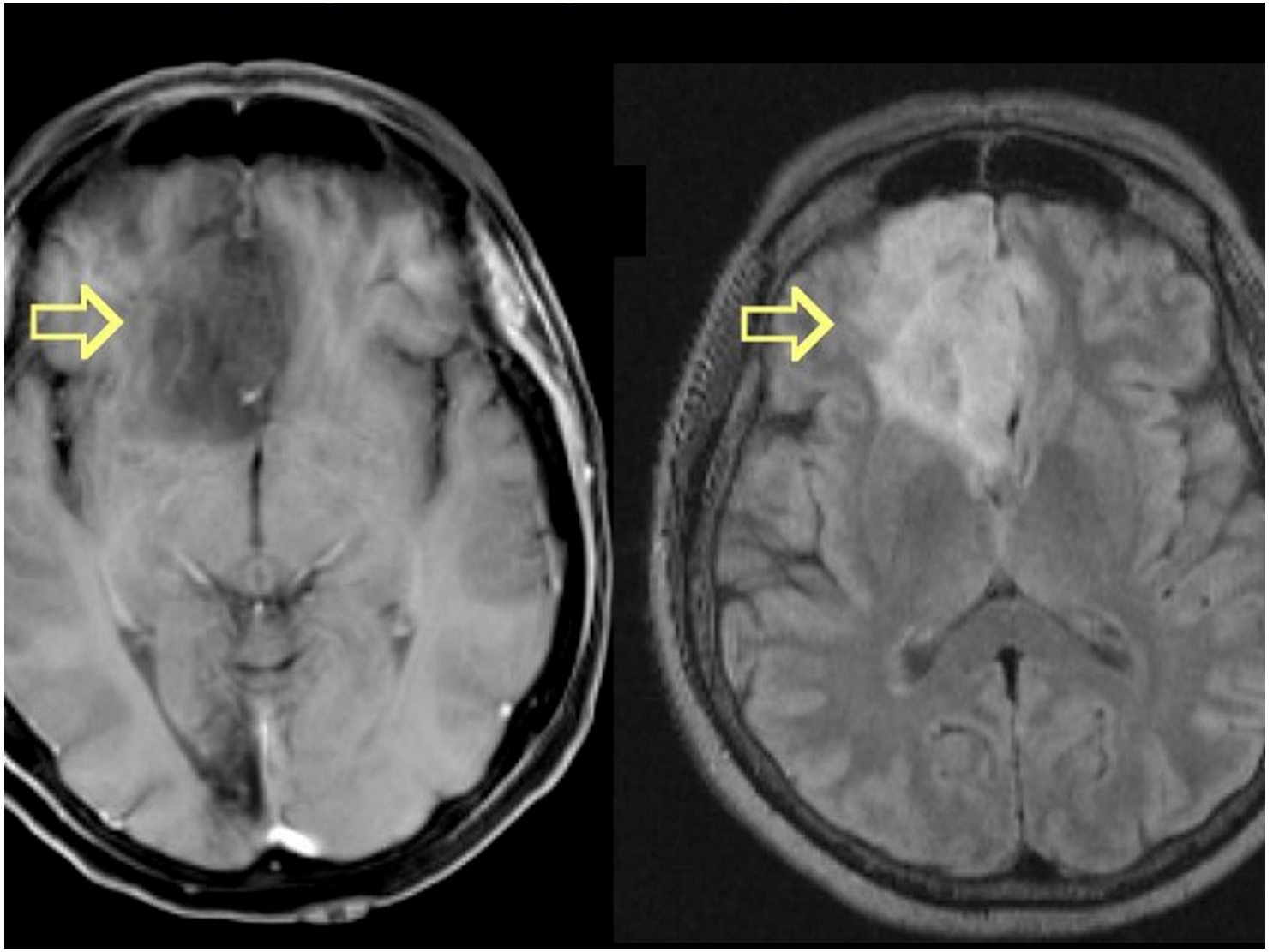
- “Fried egg”
- Peri-nuclear halos

Uptodate.com

Increased signal T2/flair

No enhancement

Calcification suggestive (1p/19q)



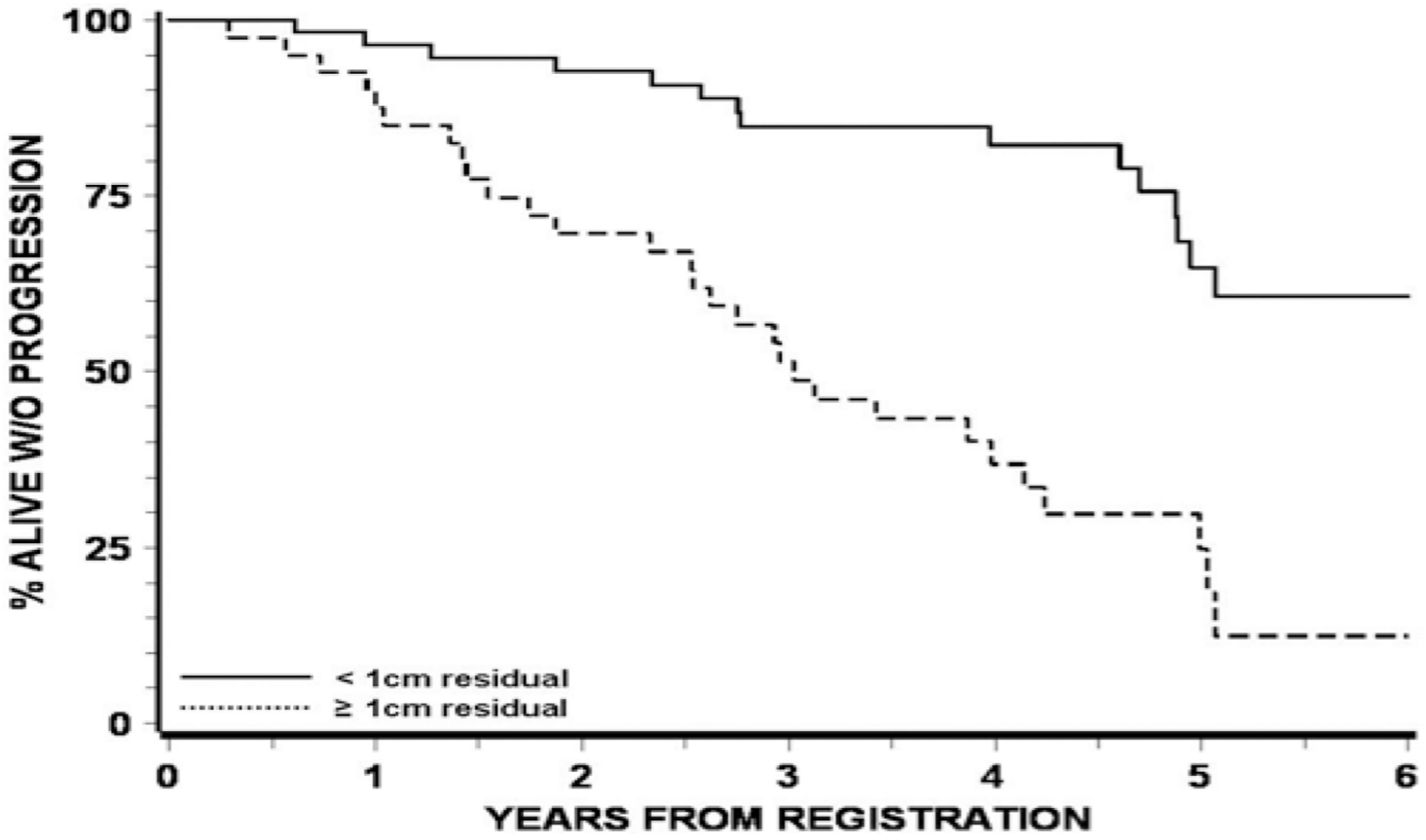
Surgery

- Diagnosis
  - Bx associated with risk of under-sampling
- Therapeutic
  - No RCT evaluating extent of resection
  - MRI correlate completeness of resection and OS
  - “Believer’s” trial

	GTR	STR	Bx
5-yr survival	75%	60%	50%

Smith JS, J Clin Oncol. 2008;26(8):1338.
Karim, A.B. et al., 1996. Radiation Oncology Biology, 36(3), pp.549–556.

Surgery:98-02



Shaw, E.G. et al., 2008.. Journal of Neurosurgery, 109(5), pp.835–841.

Dose

NCCTG/RTOG/ECOG (Intergroup 86-72-51)

	50.4 Gy	64.8	P value
5-yr OS	72%	65%	0.48
5- yr PFS%	~50	~50%	0.65

EORTC "Believers" Trial 22844

	45 Gy	59.4 Gy	P value
5-yr PFS	47%	50%	0.94
5-yr OS	58%	59%	0.73

Karim, A.B. et al., 1996.. Radiation Oncology Biology, 36(3), pp.549–556.
Shaw, E., 2002. JCO20(9), pp.2267–2276.

EORTC "non-believers" Trial 22845

	Surgery alone	Adjuvant RT	p value
5-yr PFS	35%	55%	<0.001
5-yr OS	66%	68%	0.87
MPFS M OS	3.3-yrs 7.4-yrs	5.3-yrs 7.2-yrs	<0.001 0.872
Seizure at 1-yr	41%	25%	0.03

Van den Bent, M.J. et al., 2005. Lancet, 366(9490), pp.985–990.

Chemotherapy

- Some LGG patients don’t do well
  - Who is at high-risk?
  - How to treat?

RTOG 98-02


Low grade Glioma
Low Risk:
<40 *and* GTR
Observation
High Risk:
≥ 40 and/or STR
RT: 54 Gy
RT: 54 Gy
→PCV x 6

RTOG 98-02
Low-risk patients

	2-yr	5-yr
PFS	82%	48%
OS	99%	93%

Shaw, E.G. et al., 2008. Journal of Neurosurgery, 109(5), pp.835–841.

98-02: Prognostic factors for PFS

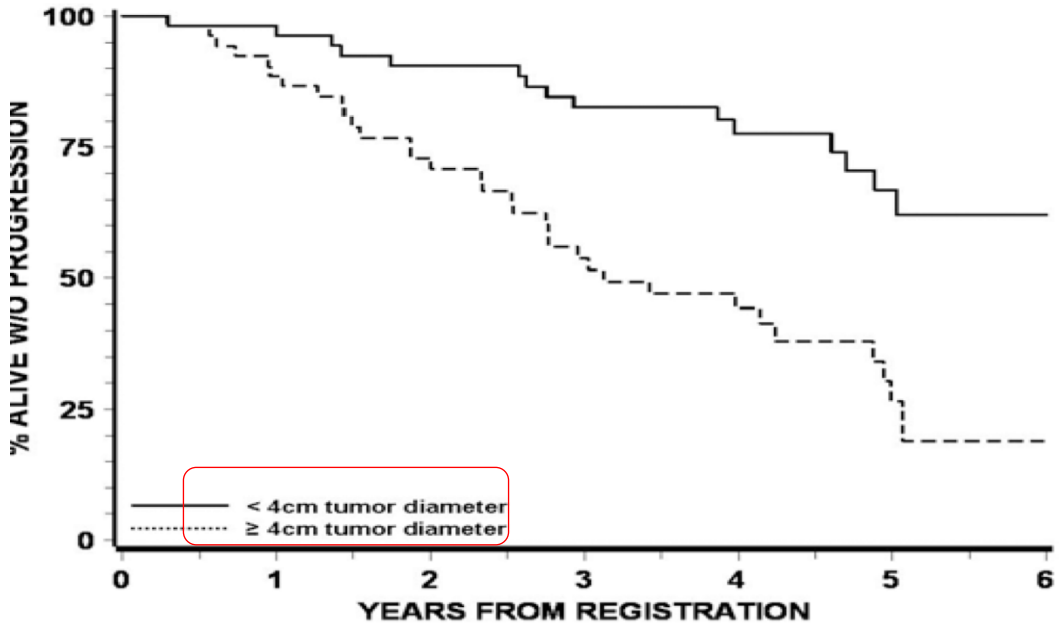
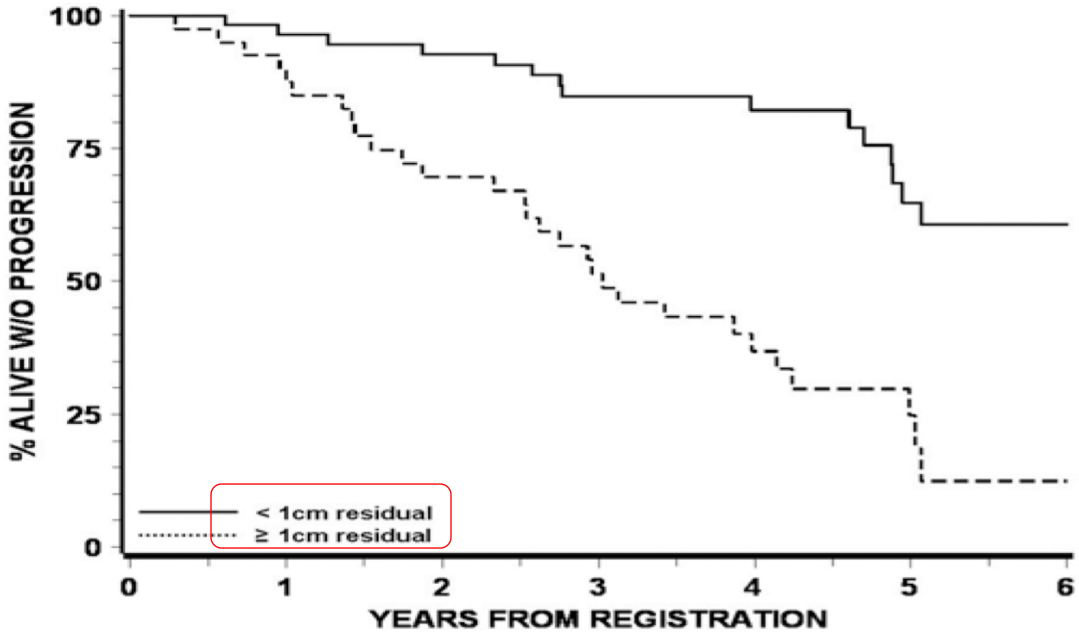
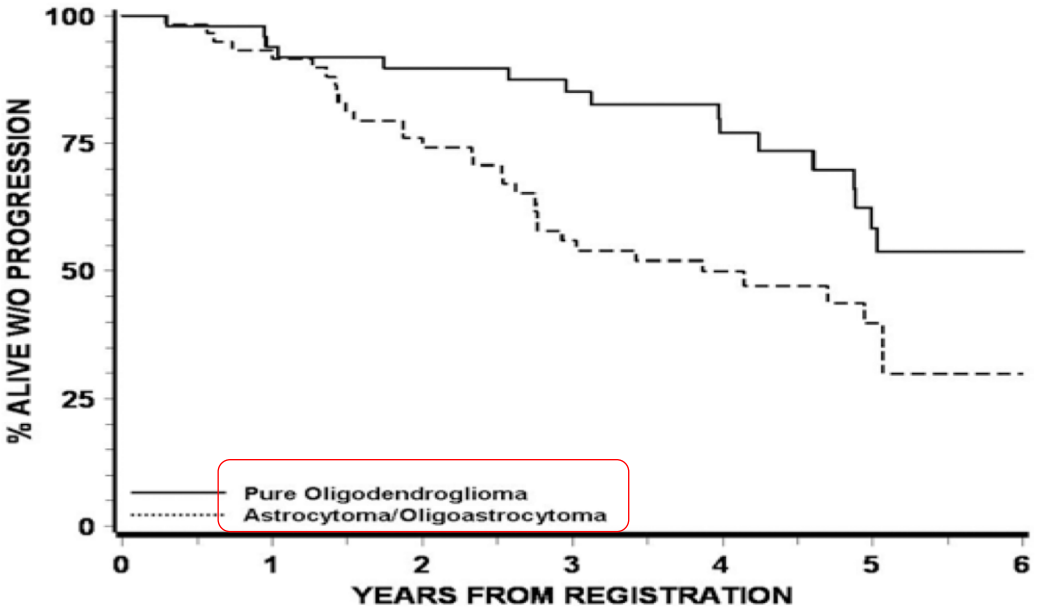


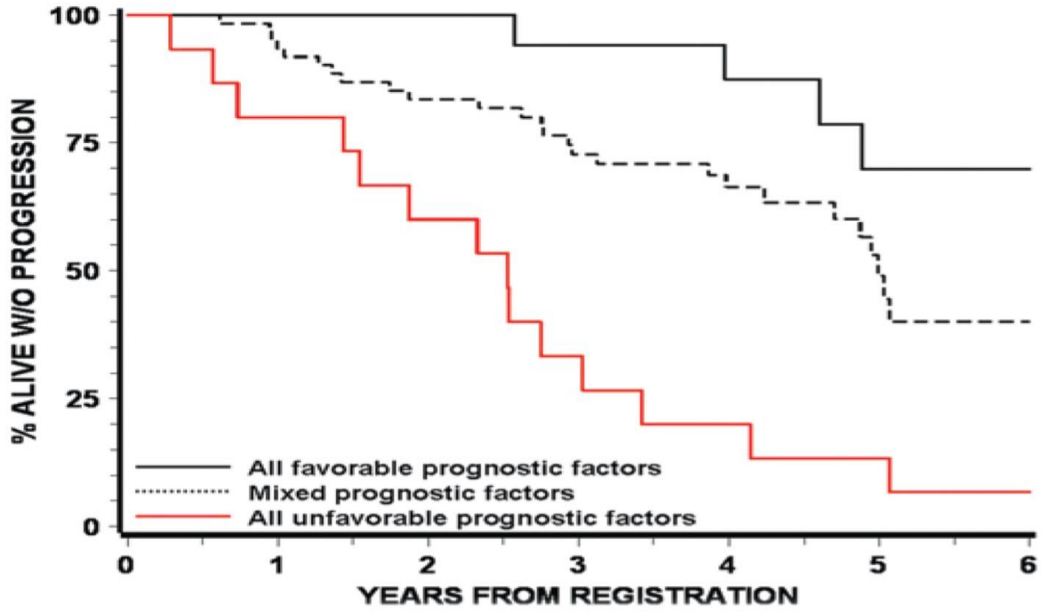
Fig. 3.
Line graph showing patient PFS according to 2 different tumor diameters (< 4 cm vs ≥ 4 cm).



Shaw, E.G. et al., 2008. Journal of Neurosurgery, 109(5), pp.835–841.

98-02 prognostic factors for PFS





5-yr pfs 70 vs 13%

Shaw, E.G. et al., 2008. Journal of Neurosurgery, 109(5), pp.835-841.

RTOG 98-02

P: 60 mg/m2; CCNU 110 mg/m2; VCR: 1.4 mg/m2

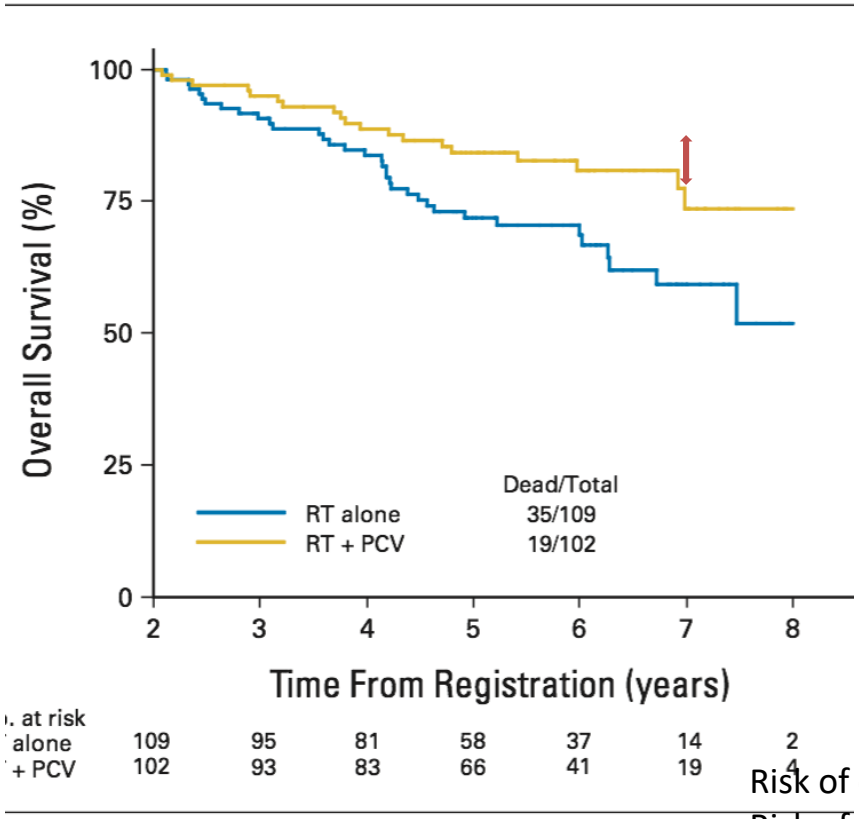
RTOG 98-02

High-risk patients surviving two years: *post hoc analysis*

Surviving additional 3 and 5-yrs

RT: 72% and 59%%

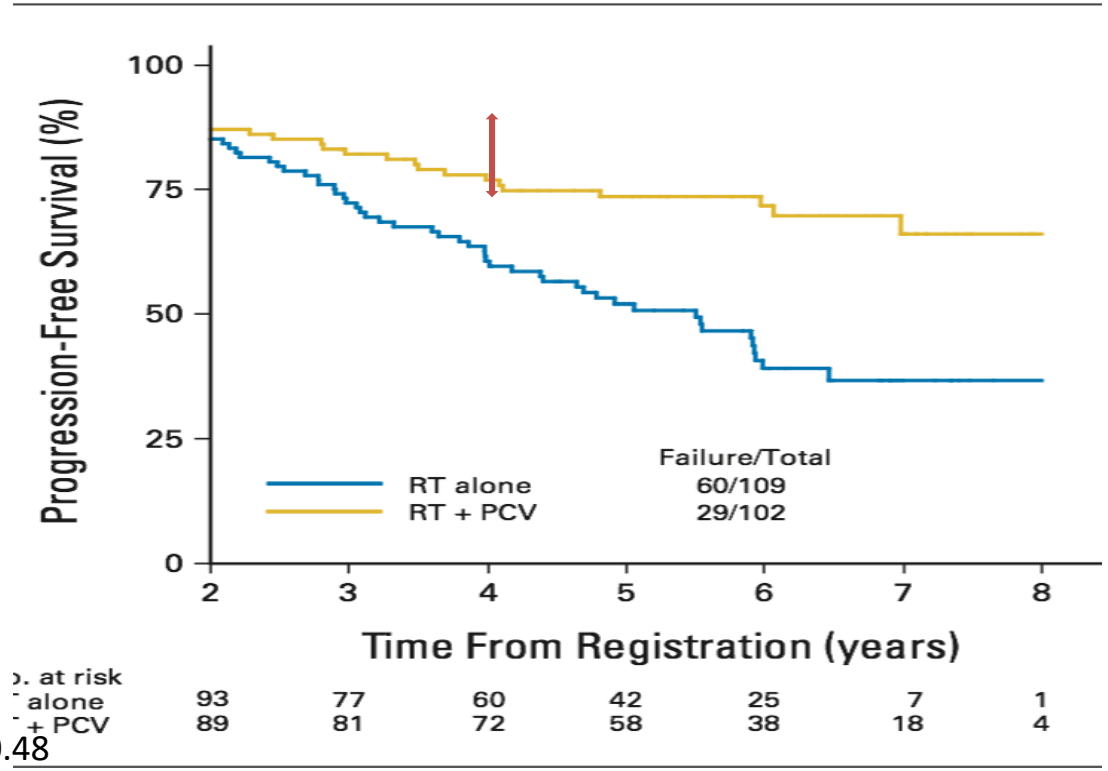
RT+PCV: 84% and 74% **p=0.02**



Surviving additional 3 and 5-yrs

RT: 52% and 37%

RT+PCV: 74% and 66% **p<0.001**



Risk of death: HR: 0.48

Risk of pregression: 0.56

Shaw, E.G. et al., 2012. *JCO*. 30(25), pp.3065–3070.

Mature Survival Data From RTOG 9802: A Phase III Study of RT with or Without Procarbazine, CCNU, and Vincristine (PCV) for Adult Patients with High-Risk Low Grade Glioma

Minesh P Mehta, Minhee Won, Edward G. Shaw, Jan C. Buckner, Mark R. Gilbert, Geoffrey Barger, Stephen Coons, Peter Ricci, Dennis Bullard, Paul D. Brown, Keith Stelzer, David Brachman, John H. Suh, Christopher J. Schultz, Jean-Paul Bahary, Barbara Jean Fisher, Harold Kim, Albert D. Murtha, Walter J. Curran Jr.

University of Maryland, MD; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Wake Forest University, NC; Mayo Clinic, MN; MD Anderson Cancer Center, TX; Wayne State University, MI; Barrow Neurological Institute, AZ; Radiology Imaging Associates, CO; Triangle Neurosurgeons, NC; Mid-Columbia Medical Center, OR; Arizona Oncology Services Foundation, AZ; Cleveland Clinic, OH; Medical College of Wisconsin, WI; Centre Hospitalier de l'Universite de Montreal, QB; London Regional Cancer Program, ON; Wayne State University, MI; Cross Cancer Institute, Edmonton, AB; Emory University, GA

Mehta ASTRO 2014

98-02

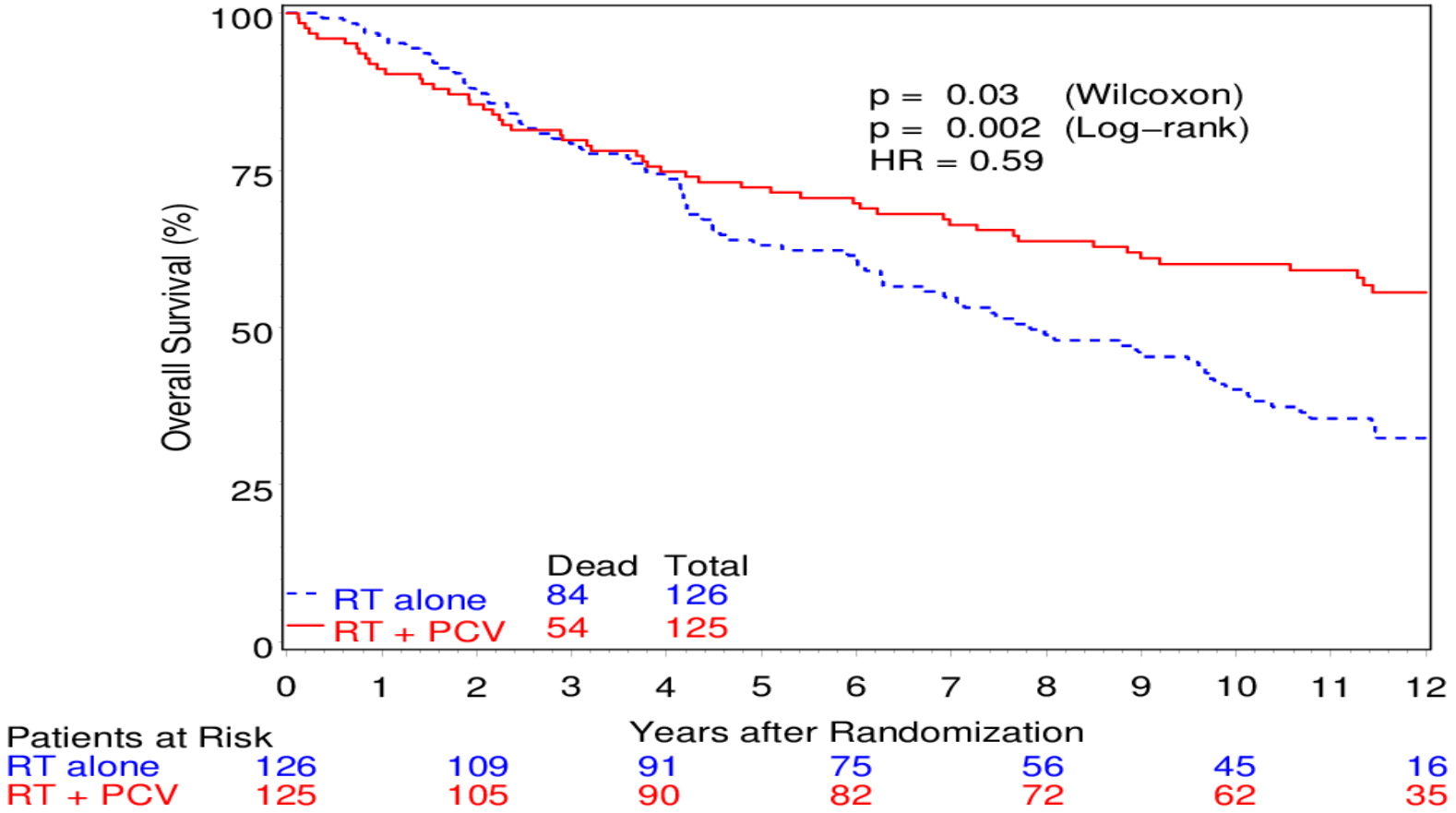
Matured results of high-risk patients

	RT	RT+PVC	P=0.001
Median PFS-yrs	4	10.4	
5-yrs (%)	44.1	61.2	
10-yrs (%)	20.9	50.5	

	RT	RT+PVC	P=0.003
Median OS-yrs	7.8	13.3	
5-yrs (%)	63.1	72.3	
10-yrs (%)	40.1	60.1	

Mehta ASTRO 2014

98-02
Matured results of high-risk patients



2012 to 2014: HR improved from .72 to .59

Minesh Mehta ASTRO 2014

2019 ASCO update

- No PCV benefit for wtIDH
- PCV benefit to mIDH both co-del and nondel
- Evolving

Bell et al ASCO 2019

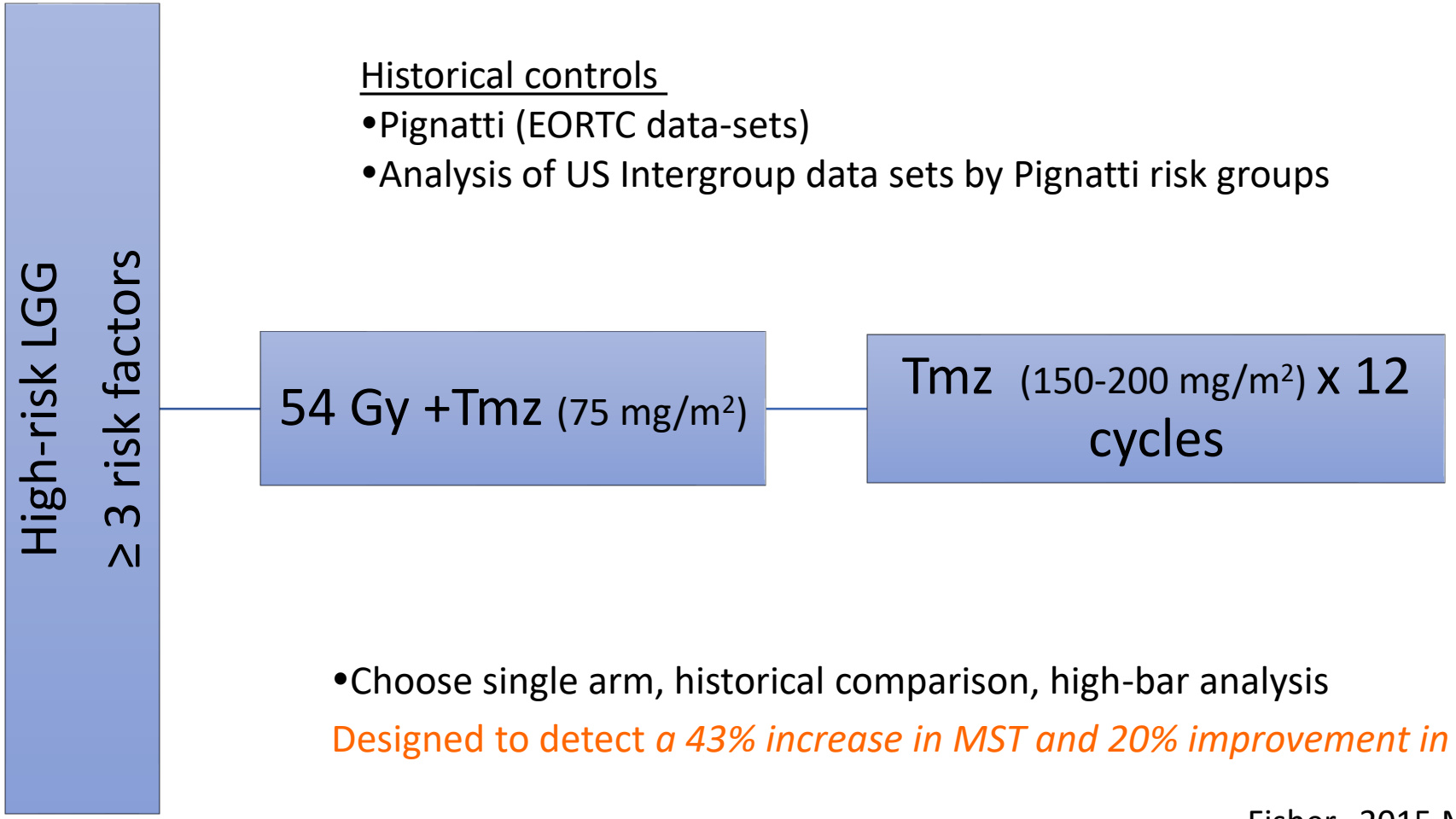
EORTC Prognostic Data-set

- ≥ 40-yr, astrocytoma histology, largest diameter ≥ 6 cm, tumor crossing midline, presence of neurologic deficit (*not sz*)

- ≥3 variables is high-risk

Pignatti, F., 2002. *JCO*, 20(8), pp.2076–2084.

RTOG 04-24



Historical controls

- Pignatti (EORTC data-sets)
- Analysis of US Intergroup data sets by Pignatti risk groups

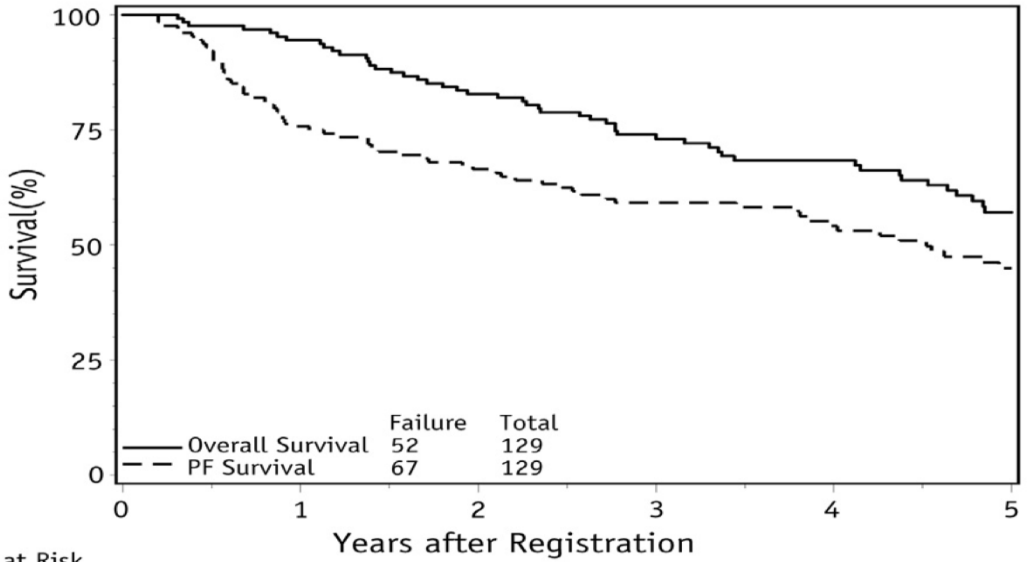
- Choose single arm, historical comparison, high-bar analysis

Designed to detect *a 43% increase in MST and 20% improvement in 3-yr OS*

Fisher, 2015 Mar 1;91(3):497-504

RTOG 04-24

- Historical MST for high-risk was 40.5
- Designed to detect 43% increase to 57.9 mos
- Detect improved 3-yr OS from 54% to 65 %

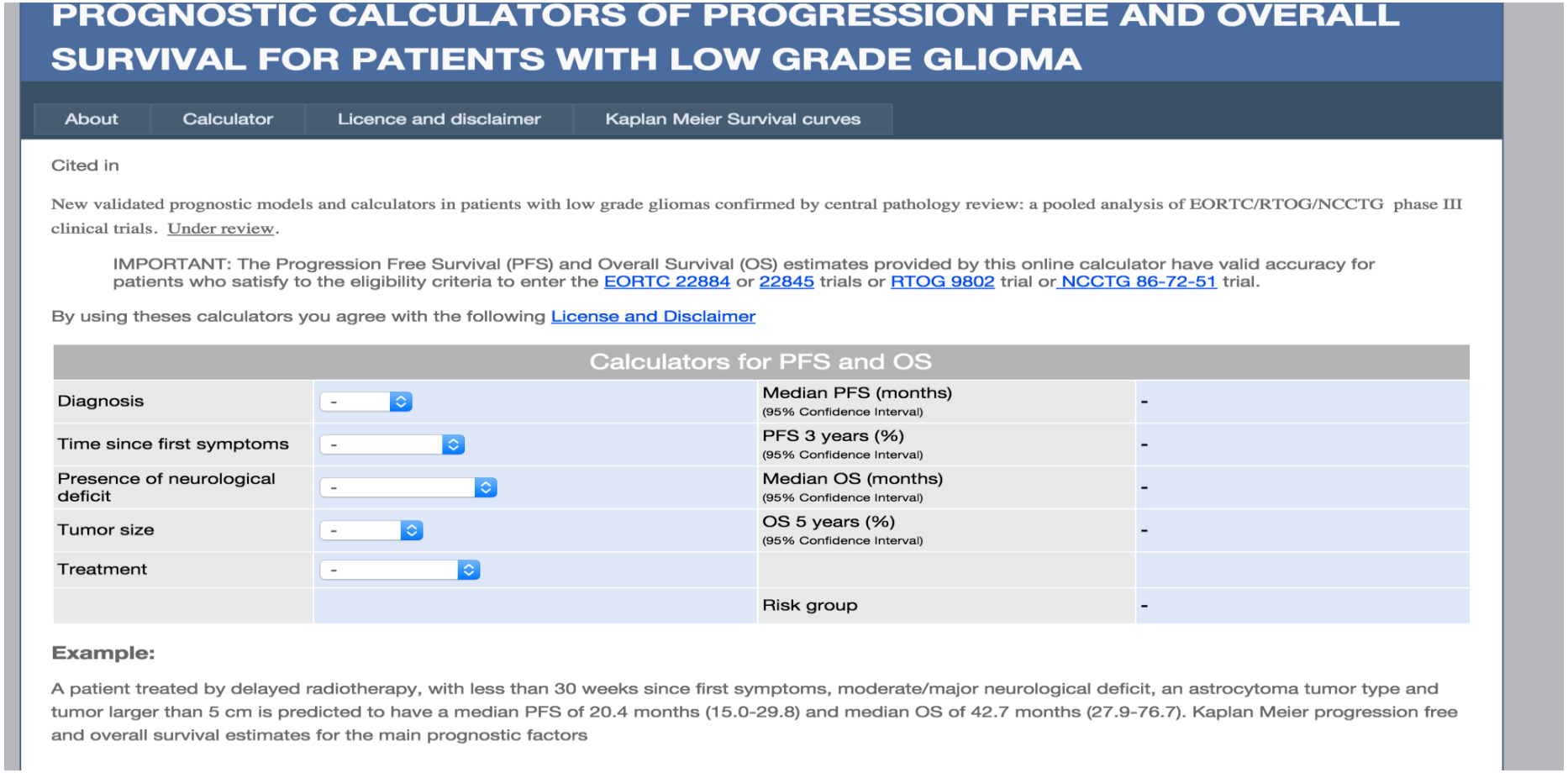


Prognostic model and calculator for LGG

- PFS and OS negatively influenced by
  - Baseline neurologic deficits
  - Time since first symptoms <30 weeks
  - Astrocytoma histopathology
  - Size > 5 cm
- PFS negatively influenced by
  - Delayed RT
- Molecular data not available for analysis

Gorlia, T. et al., 2012.Neuro-oncology 48(8), pp.1176–1184.

Prognostic calculator



PROGNOSTIC CALCULATORS OF PROGRESSION FREE AND OVERALL SURVIVAL FOR PATIENTS WITH LOW GRADE GLIOMA

About | Calculator | Licence and disclaimer | Kaplan Meier Survival curves

Cited in

New validated prognostic models and calculators in patients with low grade gliomas confirmed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. Under review.

IMPORTANT: The Progression Free Survival (PFS) and Overall Survival (OS) estimates provided by this online calculator have valid accuracy for patients who satisfy to the eligibility criteria to enter the EORTC 22884 or 22845 trials or RTOG 9802 trial or NCCTG 86-72-51 trial.

By using theses calculators you agree with the following License and Disclaimer

Calculators for PFS and OS			
Diagnosis	-	Median PFS (months) (95% Confidence Interval)	-
Time since first symptoms	-	PFS 3 years (%) (95% Confidence Interval)	-
Presence of neurological deficit	-	Median OS (months) (95% Confidence Interval)	-
Tumor size	-	OS 5 years (%) (95% Confidence Interval)	-
Treatment	-		
		Risk group	-

Example:

A patient treated by delayed radiotherapy, with less than 30 weeks since first symptoms, moderate/major neurological deficit, an astrocytoma tumor type and tumor larger than 5 cm is predicted to have a median PFS of 20.4 months (15.0-29.8) and median OS of 42.7 months (27.9-76.7). Kaplan Meier progression free and overall survival estimates for the main prognostic factors

http://www.eortc.be/tools/lggcalculator/calculator.aspx

Gorlia, T. et al., 2012.Neuro-oncology 48(8), pp.1176–1184.

Biomarkers for LGG

- No mature data on role for bio-markers
  - EORTC 22033 maturing

*Cairncross, J.G. et al., 1998. JNCI, 90(19), pp.1473–1479.
Jenkins, R.B. et al., 2006. Cancer Research, 66(20), pp.9852–9861.

Treatment planning

- GTV: Post-operative MRI T2 weighted image and surgical cavity
- PTV: GTV + 2 cm margin
- Dose 5040-5400 cGy/180 cGy
- Chiasm/ON <5400 cGy
- Globes/Retina <4500 cGy
- Brainstem: no hot spots

Controversies

- If initially low-risk, what about at recurrence?
- Resect again?
- Does this modify risk moving forwards?
  - If <40 and repeat GTR is still low risk?
  - If > 40 or no repeat GTR treat as high-risk?
- Dose for “high-risk”?

Brain Metastasis

Brain Metastasis

- 30% of cancer patients
  - 100-175K new cases/yr
- Increasing with improved systemic therapy
  - Lung: 50%
  - Breast:15%
    - H2N (+)
  - Unknown Primary: 10%
  - Melanoma: 5%
  - Colon/Rectum: 5%
- Best supportive care
  - Survival 1-2 mos

Site Specific GPA

- Breast Cancer

Variable	0	0.5	1.0	1.5	2.0
KPS	≤50	60	70-80	90-100	-
Subtype	Basal (-/-/-)	-	Luminal A (+/+/-)	Her2 (-/-/+)	Luminal B (+/+/+)
Age	≥60	<60	-	-	-

Sperduto, P.W. et al., 2011. Effect of Tumor Subtype on Survival and the Graded Prognostic Assessment for Patients With Breast Cancer and Brain Metastases. International journal of radiation oncology, biology, physics.

GPA breast cancer

Group	Breast-GPA	%	MST (mos)	1-yr OS	2-yr OS	3-yr OS
1	0-1	6	3.4	15	0	0
2	1.5-2.0	25	7.7	32	13	6
3	2.5-3.0	35	15	55	29	19
4	3.5-4.0	33	25	77	53	31

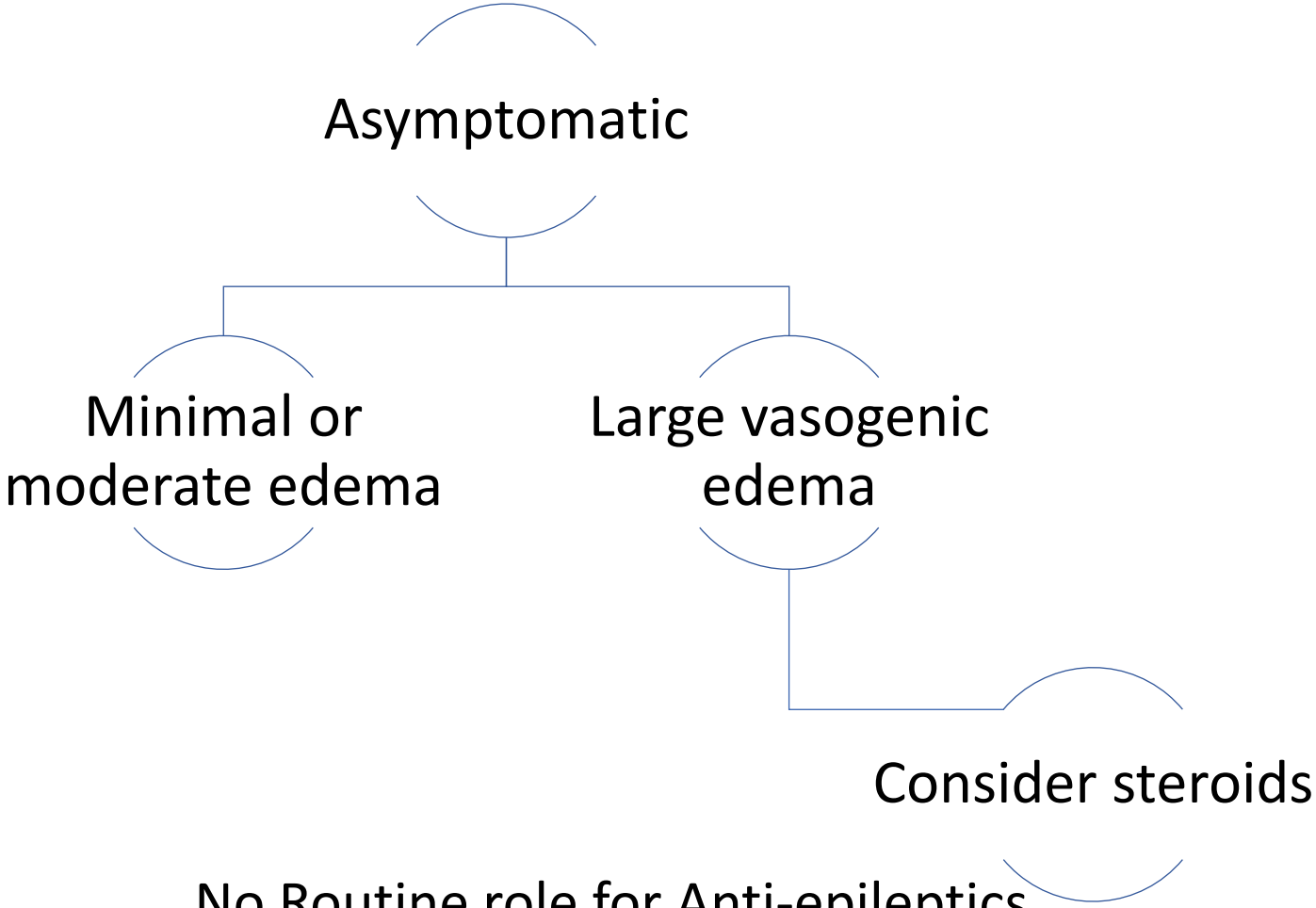
Sperduto, P.W. et al., 2011. Effect of Tumor Subtype on Survival and the Graded Prognostic Assessment for Patients With Breast Cancer and Brain Metastases. International journal of radiation oncology, biology, physics.

GPA Lung Cancer

	GPA Scoring Criteria[a]		
Prognostic Factor	**0**	**0.5**	**1.0**
Age, y	≥70	<70	NA
KPS	<70	80	90-100
ECM	Present		Absent
Brain metastases, No.	>4	1-4	NA
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos
Total	NA	NA	NA

Sperduto et al JAMA Onc 2017 Jun 1;3(6):827-831

Asymptomatic



Symptomatic

- Headaches- 40-50%
  - New onset, new pattern, associated symptoms
  - Worse in am or positional (dependent)
  - Increasing in frequency
  - *Sudden severe headache*-hemorrhage
    - *Most common primaries to bleed: Renal, melanoma, thyroid, choriocarcinoma*
    - *Highest incidence: lung*

Steroid Management

- *Symptomatic* vasogenic edema:
  - Profound symptoms:
    - Dexamethasone load 10 mg
    - → 4 mg qid or 8 mg bid
  - For most patients, 4-8 mg/day is sufficient
  - Titrate down as tolerated
  - GI prophylaxis for all patients
    - PPI
    - Standard doses of H2 blockers not effective

Steroid Management

- Screen for elevated glucose
- On steroids >4-6 weeks give PJP prophylaxis
  - Bactrim DS TIW; Atovaquone; pentimadine
- Steroid myopathy-proximal muscles
  - May confound interpretation of edema related symptoms
  - Consider converting to dose-equivalent prednisone

Steroid Management

- Steroid withdrawal syndrome
  - Myalgias, arthalgias, headache and lethargy
  - Raise dose and taper more slowly
- Adrenal insufficiency
  - Needs replacement of basal steroid requirement
  - Hydrocortisone
  - Endocrine consult
  - Education about stress doses

Management

- Long term steroid use
  - Difficulty tapering steroid due to persistent edema, consider celecoxib (COX-2) inhibitor*
  - Corticorelin acetate**
- Seizure
  - 500 mg IR levetiracetam bid if evidence of seizure
  - May slowly titrate up to 1500 mg bid

*Portnow J, Suleman S, Grossman SA, Eller S, Carson K. Neuro Oncol. 2002;4(1):22.; **Recht L, 2013;31(9):1182-1187.

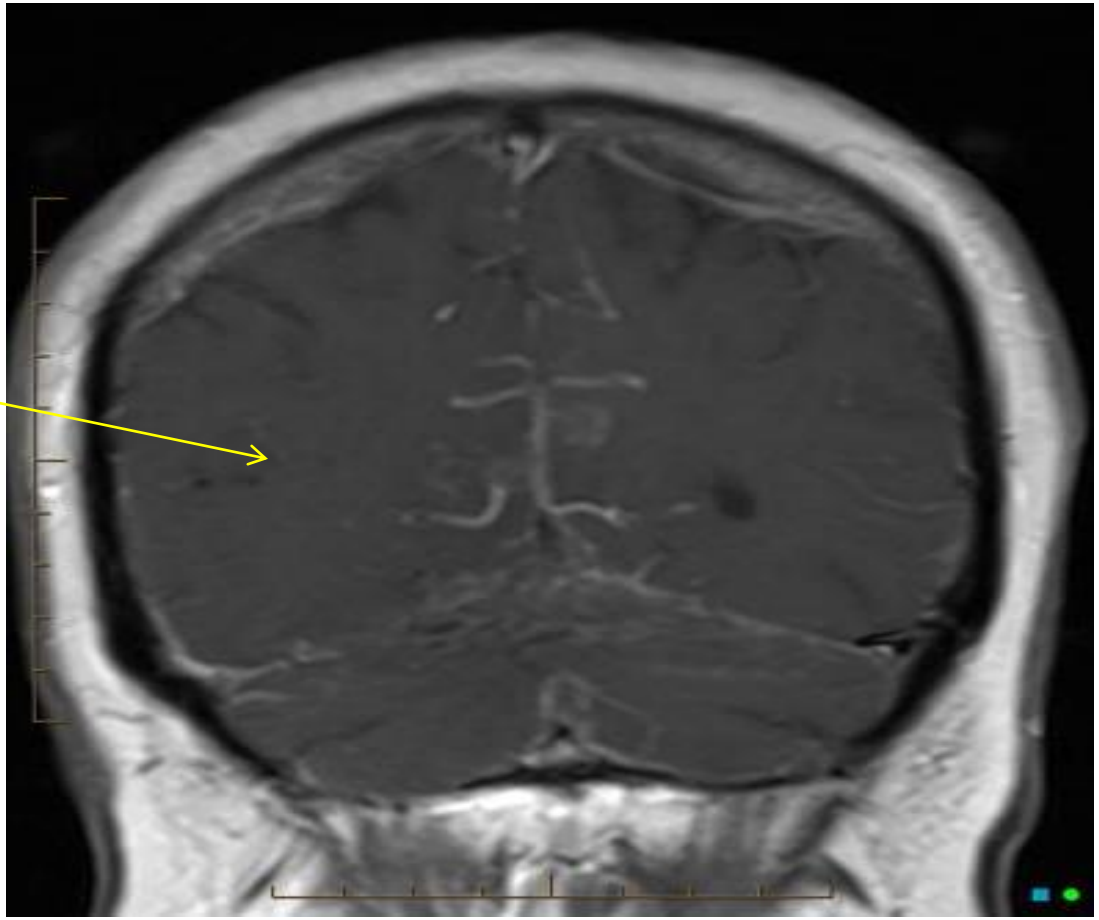
Management

- Seizure
  - Pre-seizure aura
    - Ativan 1mg dissolve sublingual prn seizure aura
    - Discuss w/neurology/neurosurgery or go to ED
  - Post-operative (SRS?) *prophylaxis*
    - keppra 500 mg po bid begin gradual taper 1-2 weeks post-operatively
- *No standard role for AED in absence of seizures*

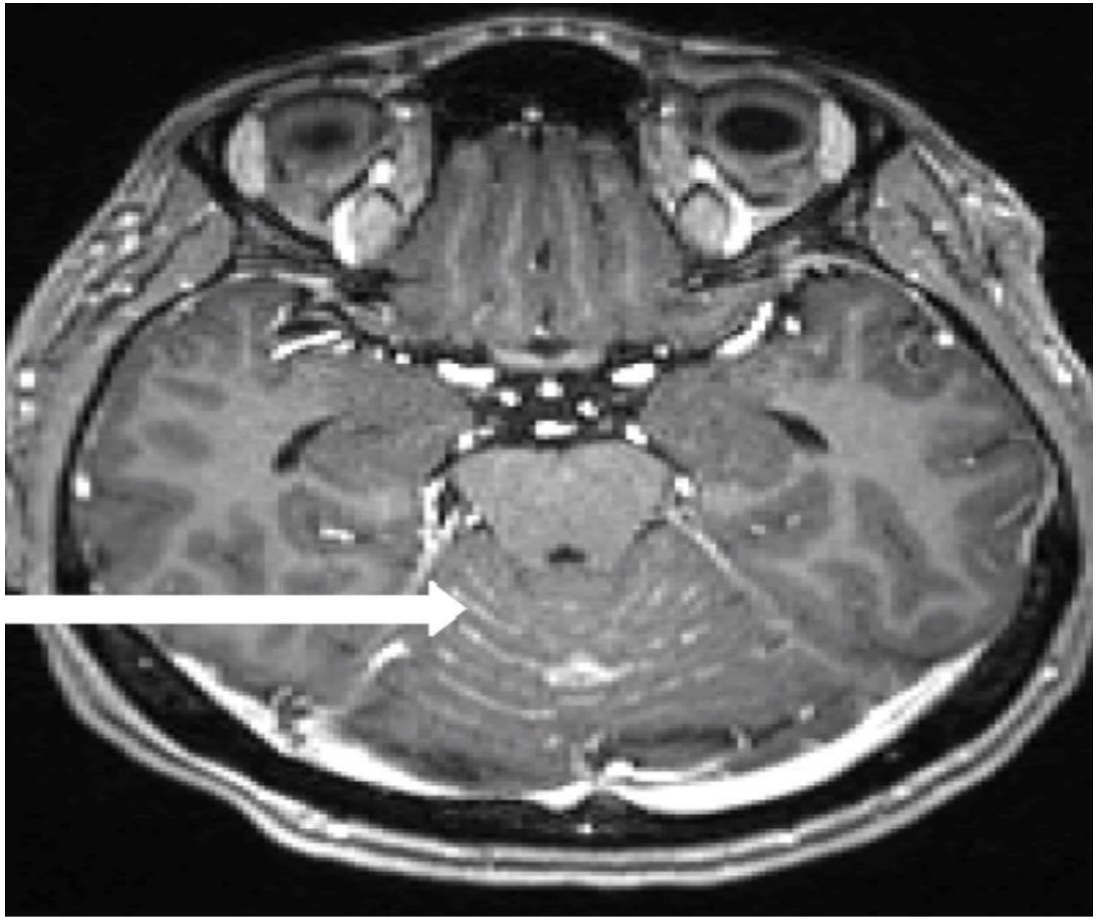
Practice parameter: Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG Neurology. 2000;54(10):1886.

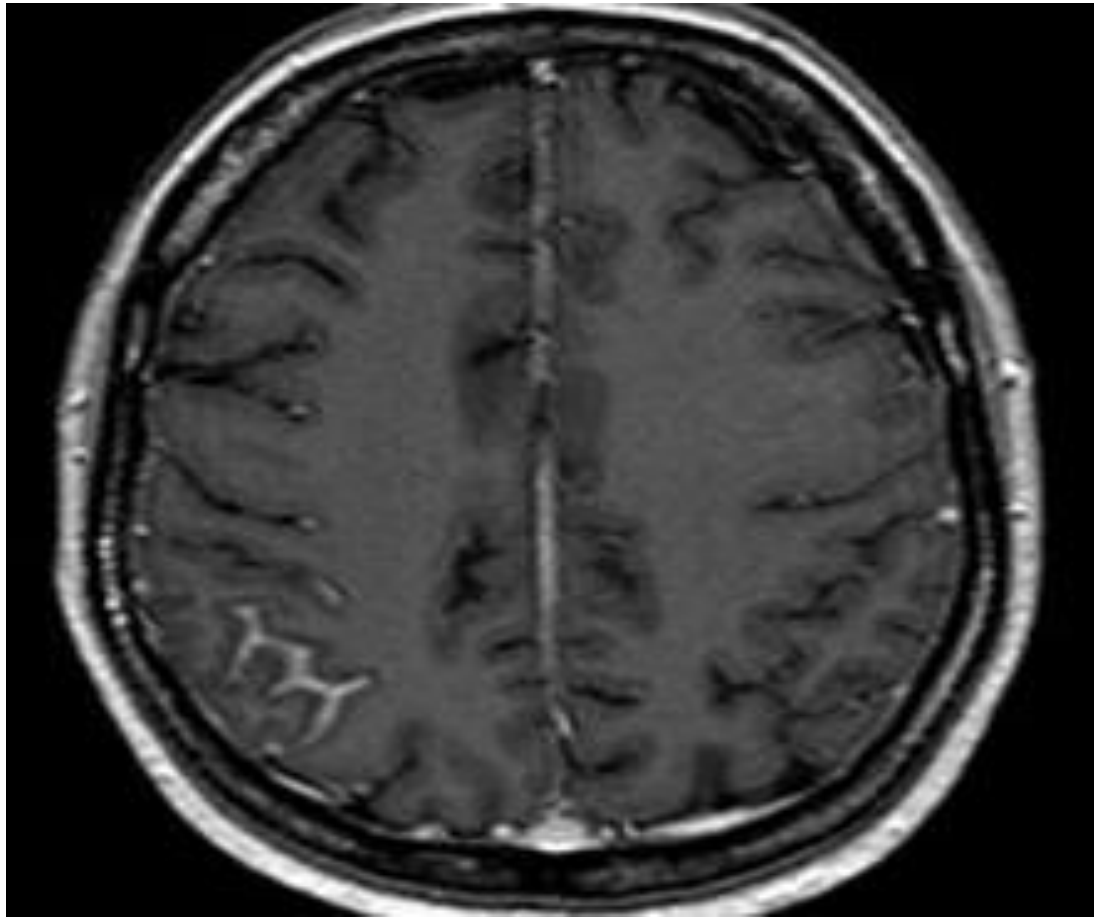
Extensive metastasis

- > 10 lesions
- Carcinomatosis
- Leptomeningeal spread
  - Carcinomatosis
  - Dural spread



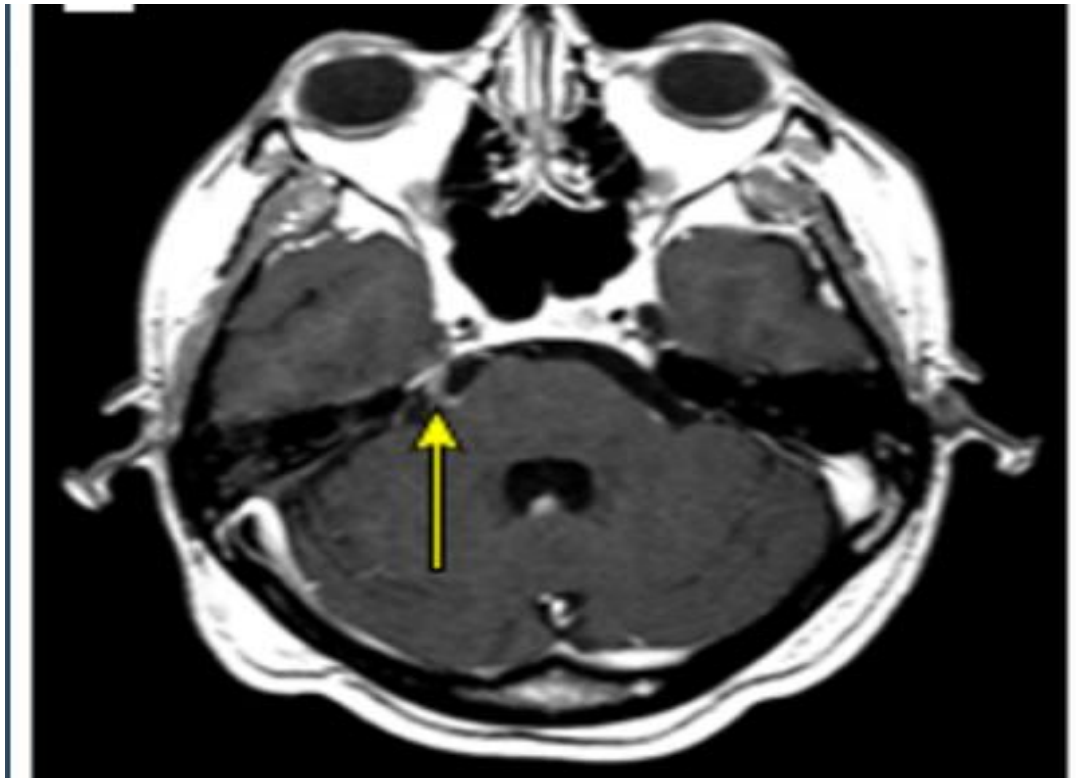
Leptomeningeal carcinomatosis



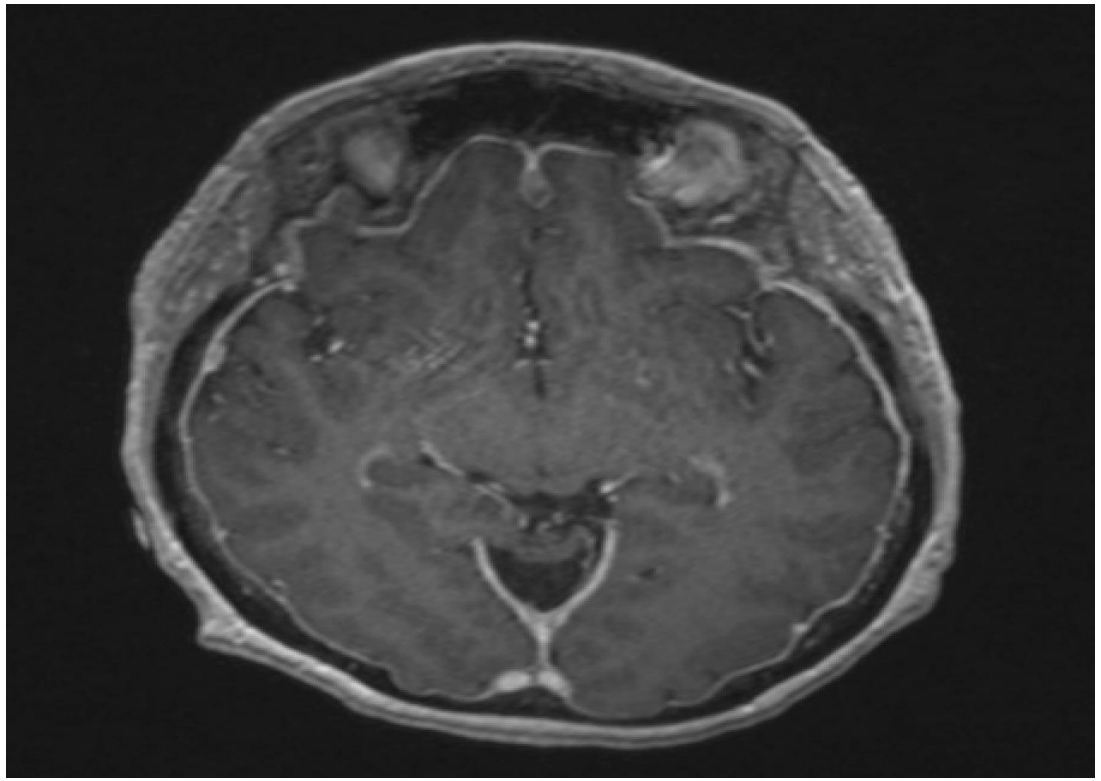


Leptomeningeal carcinomatosis

Cranial nerve involvement



Dural (pachymeningeal) disease



Leptomeningeal carcinomatosis

- Diagnosed in 5% patients, actual ≥ 20%
- Symptoms may not focally correlate w/MRI
- May not be relieved with steroid
- Show up on MRI only 50% of the time
- Single (+) LP 50 % of the time:
  3 negative LP's required to be "true" negative
  High protein; lymphocytic pleocytosis; low glucose *suggestive*
  Will results will change management.

- Indication for full axis MRI

Leptomeningeal carcinomatosis

- Exam -dysfunction beyond symptoms
- HA- 50%
  - Increased pressure +/- hydrocephalus
    - Hydro can develop over time. VP shunt
  - Meningeal irritation

Leptomeningeal carcinomatosis

- Cranial neuropathies
- Seizures/altered mental status
- Spine symptoms

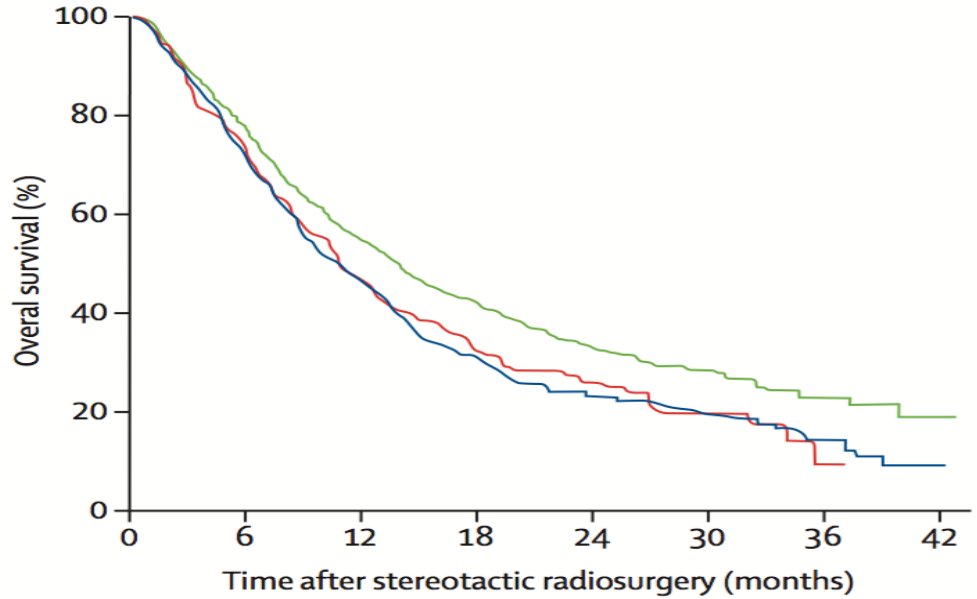
- 50% sensitivity on MRI
  - MRI post-LP risk false positive from low pressure

Leptomeningeal carcinomatosis

- High risk for hydrocephalus
  - Be alert for N/V/HA
  - Requires urgent neurosx consult/shunt
- Risk may be greater
  - After resection
  - Piece-meal resection
  - Location by dura
  - Breast cancer Posterior fossa +/- resection

5- 10 Lesions

1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk

1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

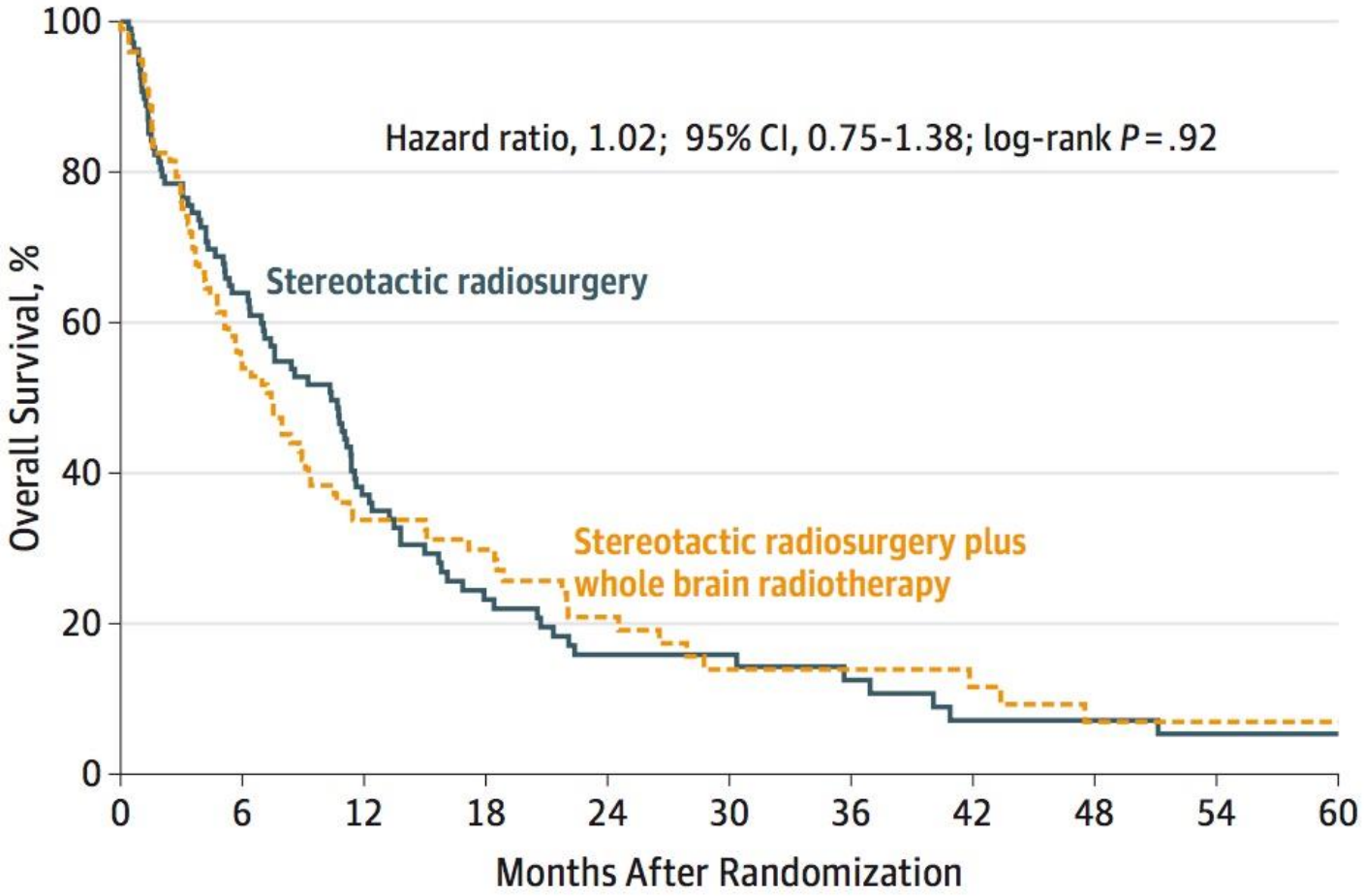
Yamamoto, M. et al., 2014. Lancet oncology, 15(4), pp.387–395.

Oligometastatic disease

- 4 randomized trials adding WBRT to SRS
- WBRT improves local and regional brain control, not OS
- WBRT adds significant neuro-cognitive toxicity
- SRS alone

Aoyama H, JAMA. 2006;295(21):2483-2491.
Chang EL Lancet Oncol. 2009;10(11):1037-1044
Kocher M . J Clin Oncol. 2011;29(2):134-141
Brown PD. JAMA. 2016;316(4):401.

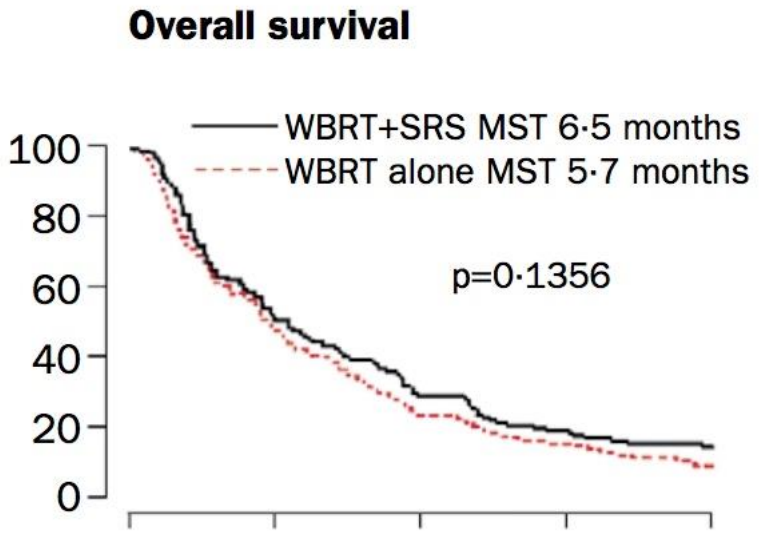
Alliance (NO574)

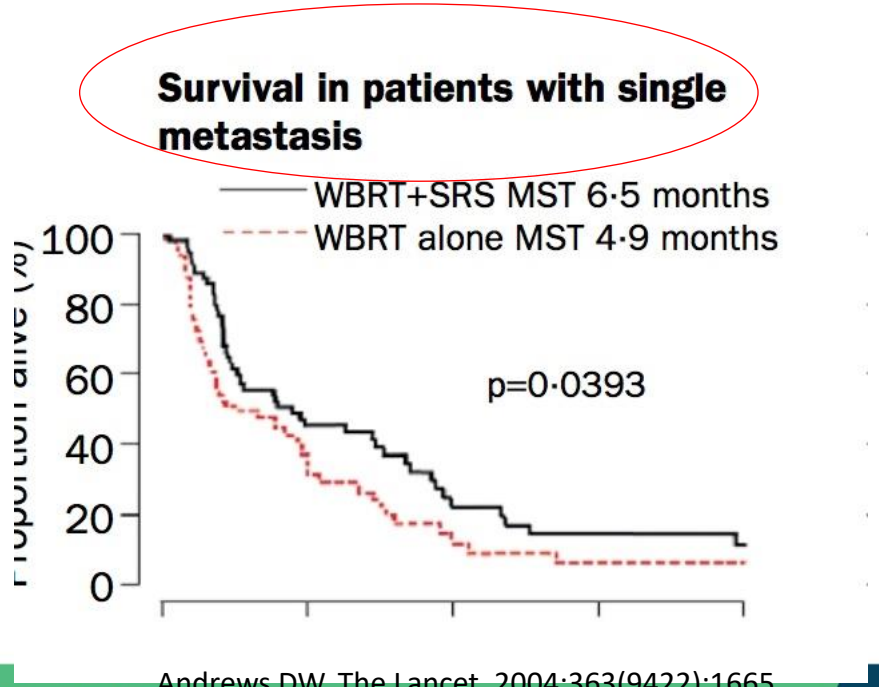


Brown PD. JAMA. 2016;316(4):401.

Oligometastatic disease

- For patients with WBRT: RTOG 95-08
- Randomized to receive WBRT (3750/250 cGy) +/- SRS





Andrews DW. The Lancet. 2004;363(9422):1665.

Oligometastatic disease

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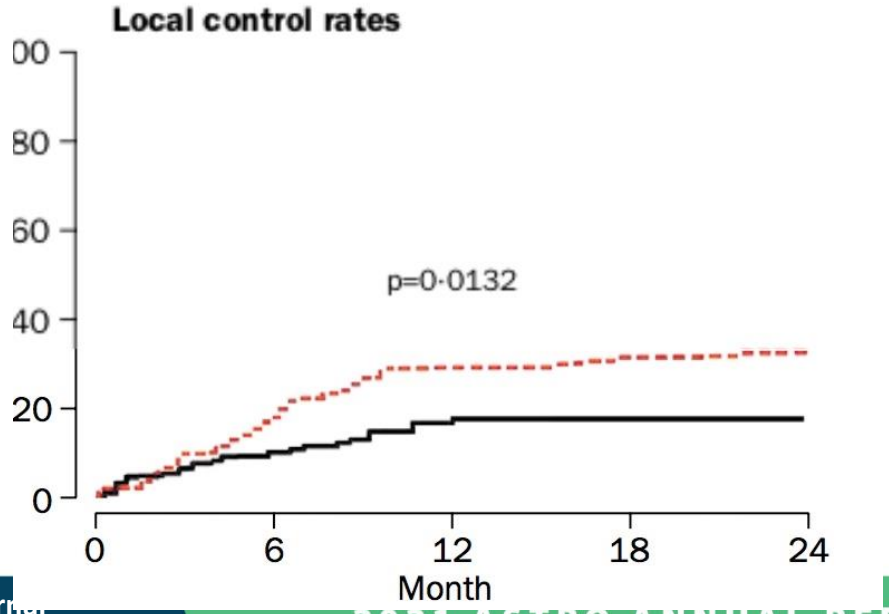
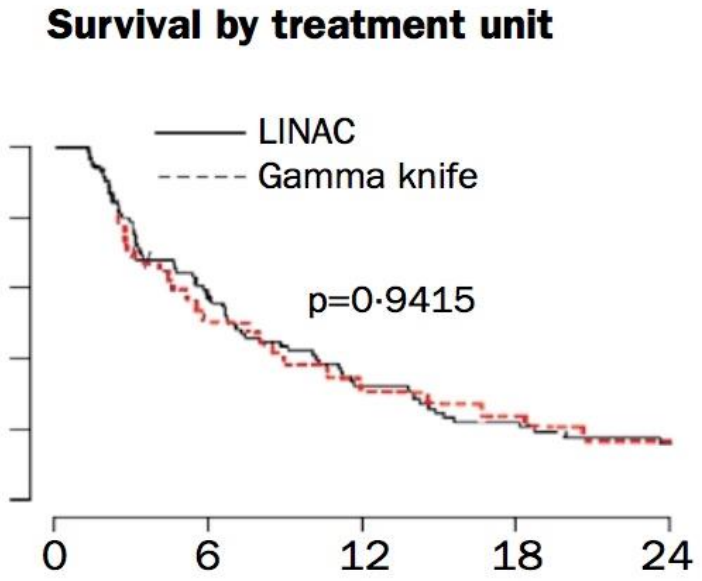
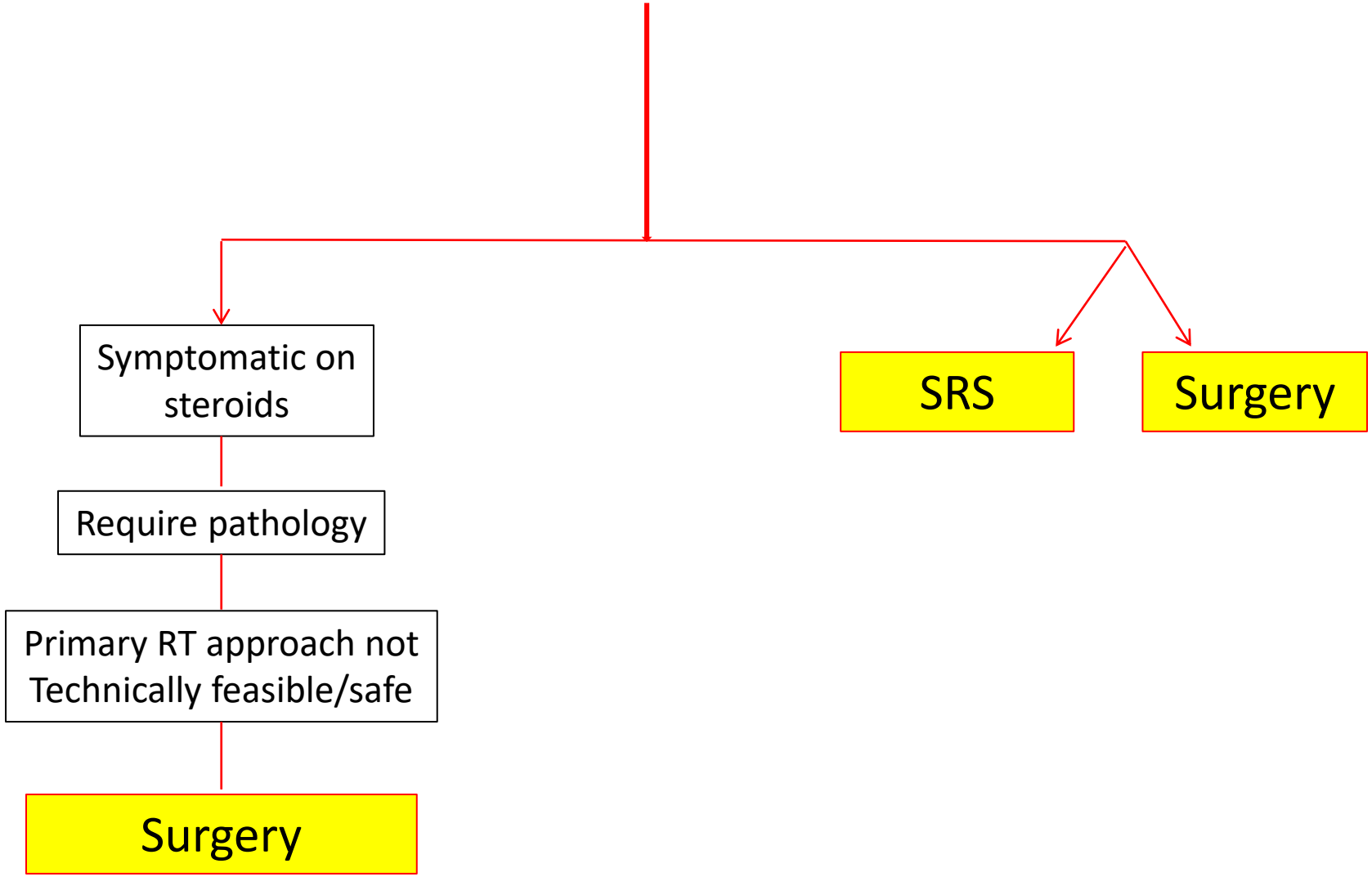




Andrews DW. The Lancet. 2004;363(9422):1665.

Single Brain Met



Single Brain Metastasis

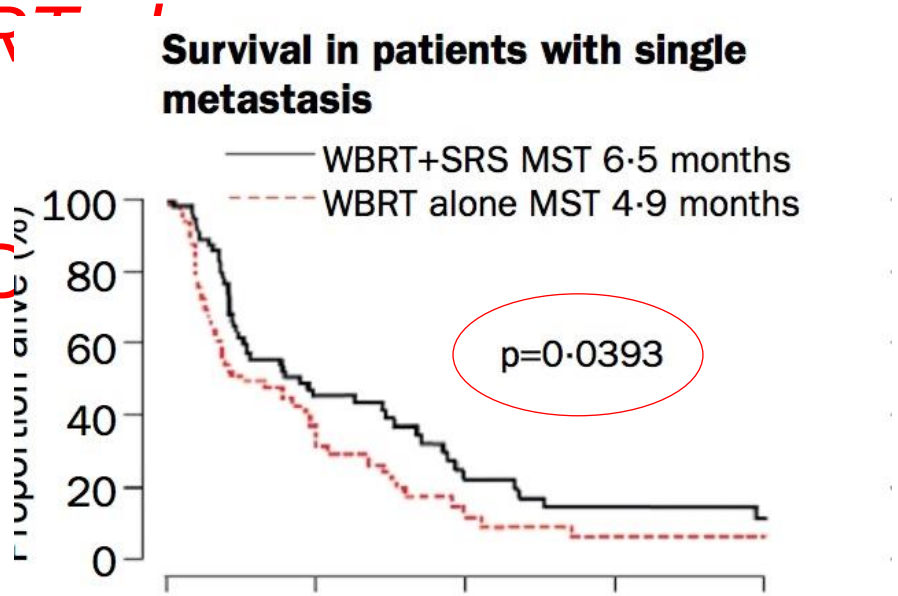
- Single: no other brain lesion
  - (Solitary: no other metastasis anywhere)
- Randomized: biopsy or resection
  - Adjuvant WBRT

	Biopsy + RT	**Surgery+ RT**	
Local recurrence	52%	20%	P<0.02
Overall survival	15 weeks	40 weeks	P<0.01
Time to Recurrence	6 months	14 months	sig
KPS>70%	8 weeks	38 weeks	P<0.005

Patchell NEJM 322(80):1990

Key Points from Surgical Papers

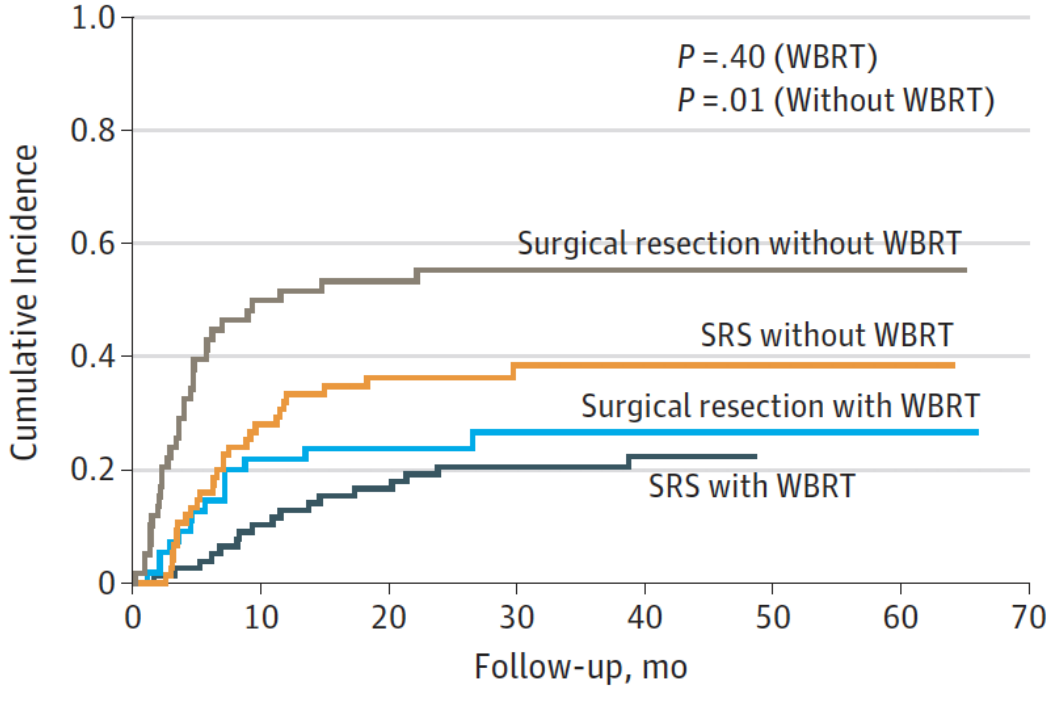
- Surgery superior for single met vs *WBRT*
  - *Not a comparison with SRS*
- Death primarily due to progressive ECD
- Likely higher risk of carcinomatosis
  - Piece-meal resection
  - Location by dura
  - Breast cancer
  - Posterior fossa +/- resection
- 11% initial patients unexpected pathology



Patchell RA. N Engl J Med. 1990;322(8):494-500
Brennan C, IJROBP 2014;88(1):130-136.
Andrews DW. The Lancet. 2004;363(9422):1665.

Single Brain Metastasis
Superiority? Surgery vs.Radiosurgery

- Stratified by receipt of WBRT
- Risk of LR higher for Sx <9 mos



Variable	HR (95% CI)	*P* Val
Surgical resection vs SRS[b]	1.15 (0.72-1.83)	.56
Time of recurrence, mo[c]		
0-3	5.94 (1.72-20.45)	.005
3-6	1.37 (0.64-2.90)	.47
6-9	0.75 (0.28-2.00)	.56
≥9	0.36 (0.14-0.93)	.04

Churilla et al 2019 Jama Onc;5(2):243-247

Postoperative WBRT

	Sx alone	Sx + WBRT	
Local recurrence	46%	10%	P<0.02
Distant brain metastasis	70%	18%	P<0.01
Overall Survival/ Independent function	-	-	ns
CNS death	44%	14%	P<0.005

Patchell et al. JAMA 280(17):1998

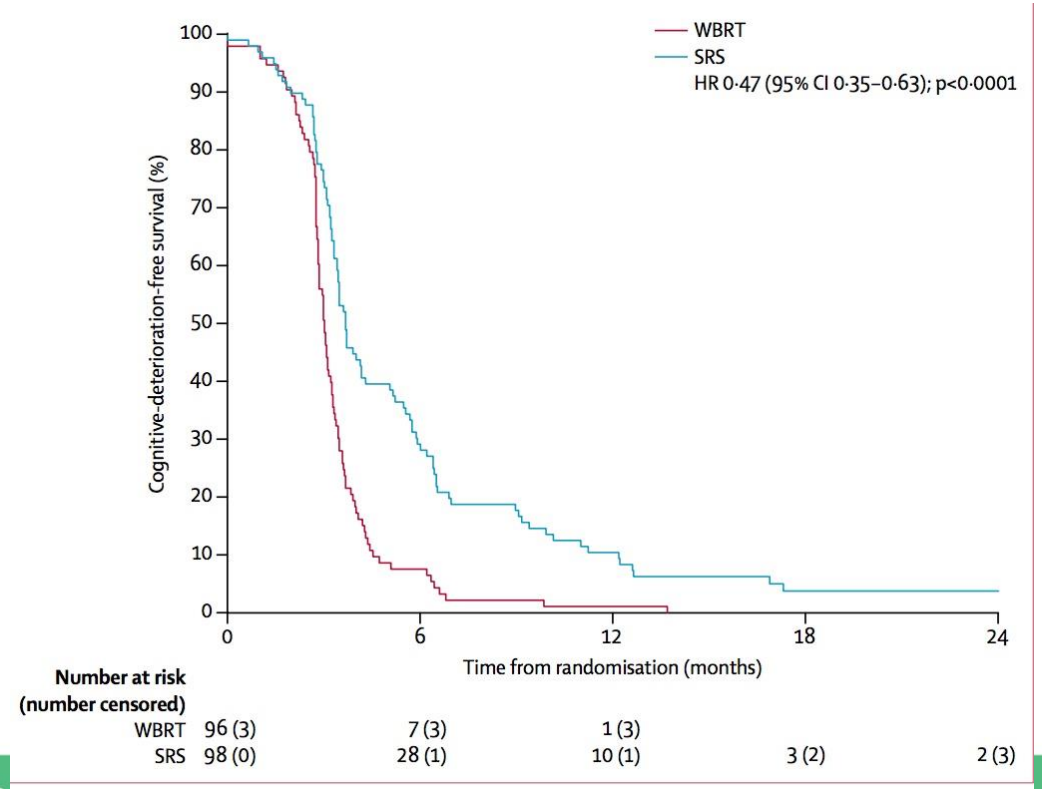
Postoperative SRS vs. WBRT

- Postoperative SRS vs. WBRT
  - Intact lesions treated with SRS
- Co-primary endpoints OS and-deterioration-free survival

Brown PD. Lancet Oncol. 2017;18(8):1049-1060.

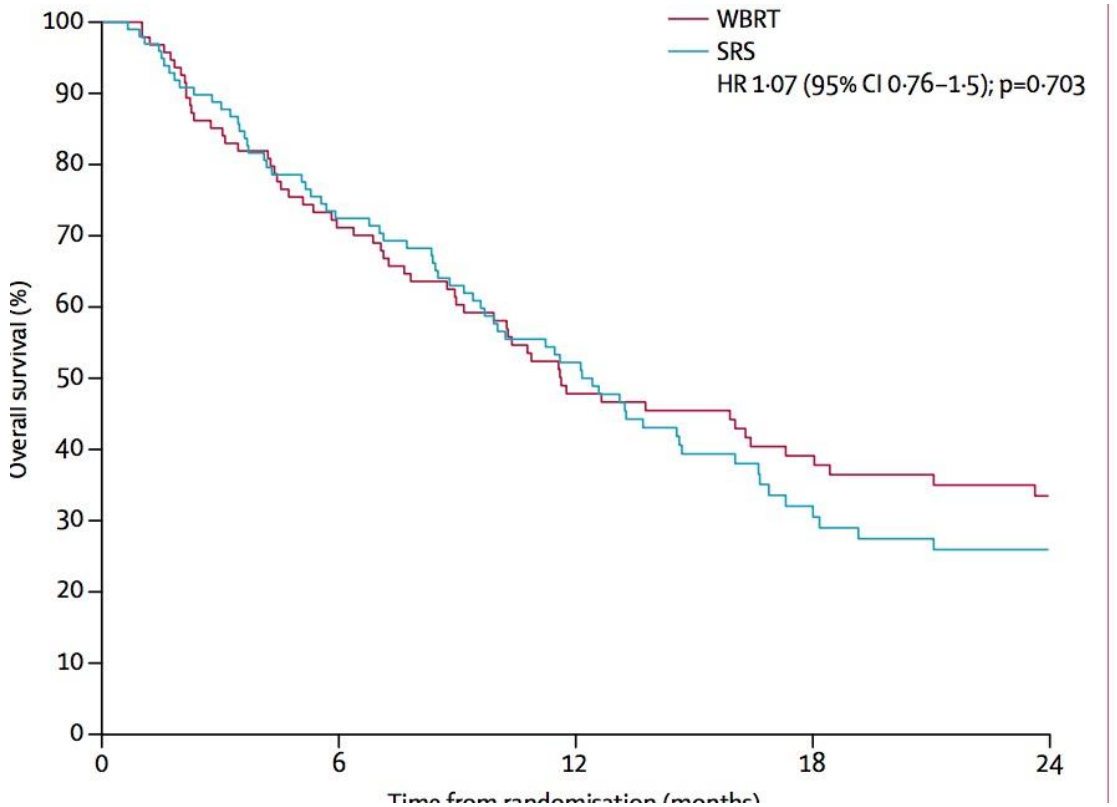
Postoperative SRS

- Median cognitive-deterioration-free survival 3.7 mos SRS vs 3.0 mos WBRT (sig)



Postoperative SRS

- No OS differences



Post-operative SRS

	Control Estimates (95%CI)		Gray's K-sample p-value
	SRS	WBRT	
Surgical Bed Control			
at 3 months	95·9% (92·0, 99·9)	93·5% (88·7, 98·7)	
at 6 months	80·4% (72·8, 88·7)	87·1% (80·5, 94·2)	p = 0·00068
at 12 months	60·5% (51·3, 71·3)	80·6% (73·0, 89·1)	

No difference in carcinomatosis

Postoperative SRS

- Improvement in physical wellbeing in SRS
- Duration of functional independence longer after SRS (nr) than WBRT (14 mos)

Postoperative SRS

- Amongst 12-mos survivors:

  Cognitive deterioration
- 3 mos- 37% SRS and 89% WBRT
- 6 mos- 46 vs. 86%
- 9 mos- 48 vs. 81%
- 12 mos-60 vs. 91%

…in spite of better local and distant control from WBRT

Following s/p SRS

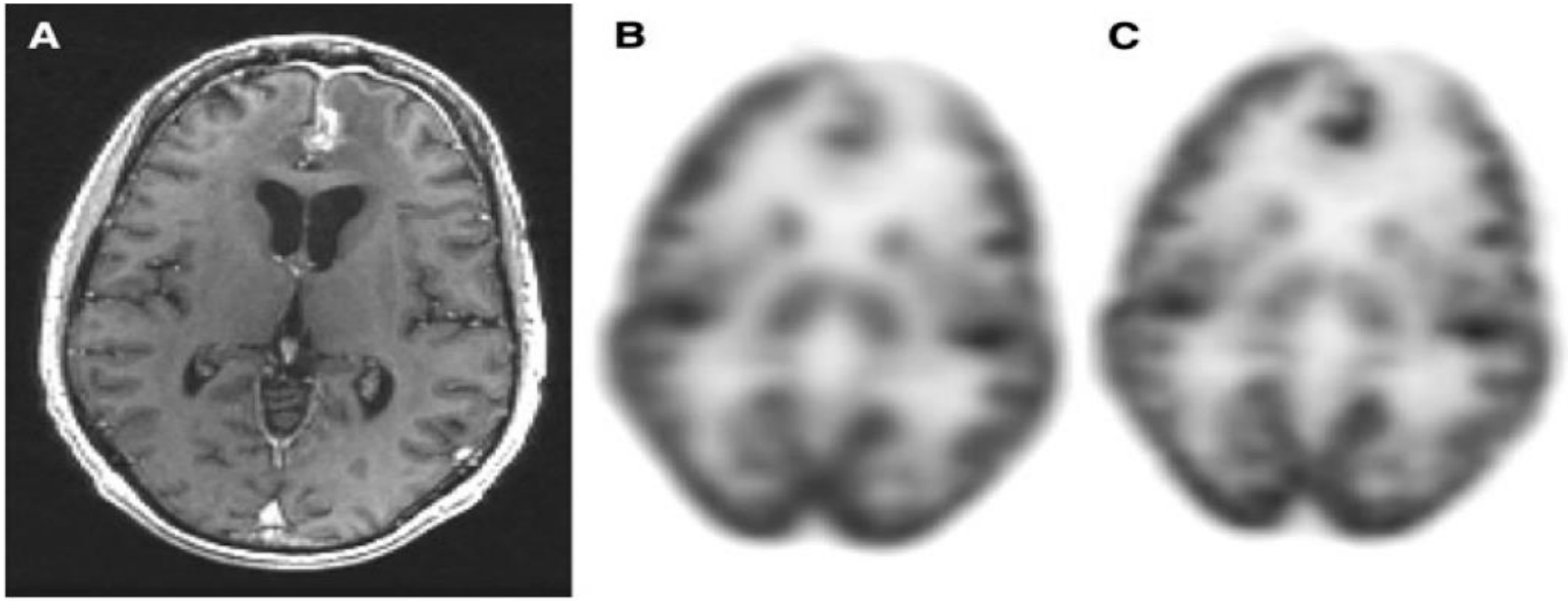
- 4-6 week f/u
- Then q 2-3 mos
- After 1 year may extend
- If relapse shorted interval
- Radionecrosis vs. Relapse is biggest challange

RN vs. Relapse

- Radionecrosis ~25%
- Symptomatic necrosis 15-20%
  - Size
  - Location-white matter
  - Number
  - V10-12 Gy
  - Biology
  - Systemic therapies
  - Host factors

Minniti, G. Radiation Oncology, 6(1), p.48;
Brennan, C. et al., 2014. 88(1), pp.130–136
Colaco RJ J Neurosurg. 2016;125(1):17-23.

Dual Phase PET scan

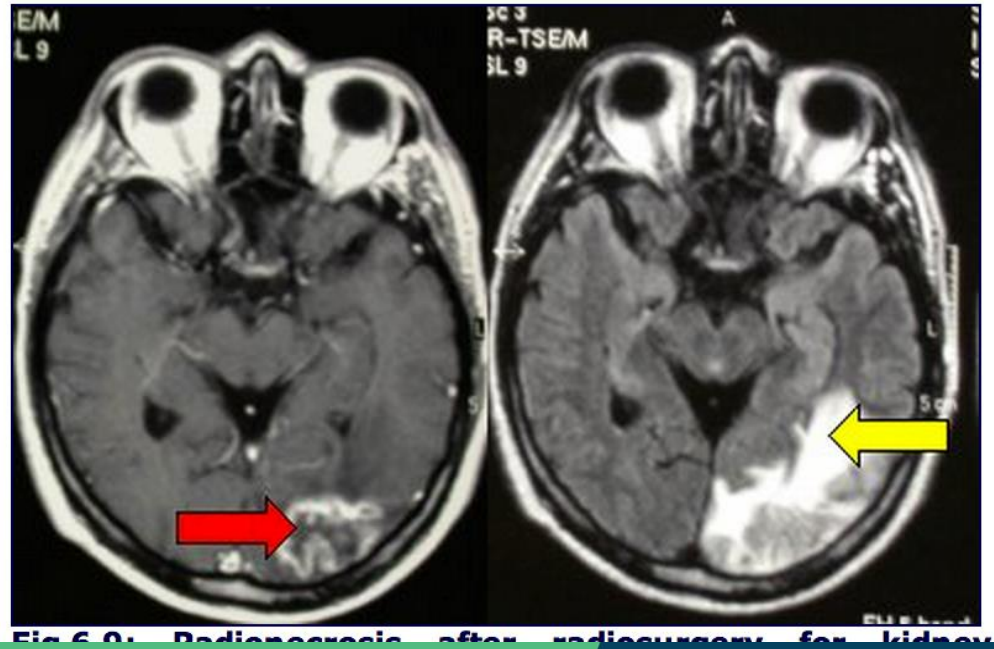


Horky, L.L. et al., 2011. Dual phase FDG-PET imaging of brain metastases provides superior assessment of recurrence versus post-treatment necrosis. Journal of neuro-oncology, 103(1), pp.137–146.

Perfusion Imaging

- Measure of relative cerebral blood volume (rCBV)
- Includes vascular transit time, CBV and cerebral blood flow
- Tumors higher rCBV, necrosis lower.

- Necrosis “feathery”, mottled, swiss-cheese pattern
- Image out of proportion to symptoms
- *Often* will stabilize



Treating Radionecrosis

- Steroid taper if symptomatic
- Repeat MRI ~4 weeks
- Surgery is diagnostic and therapeutic
- Bevacizumab:
  - Randomized trial
  - Clinical and radiographic response:
    - 0% placebo pts
    - 100% bevacizumab

Levin, V.A. et al., 2011. 79(5), pp.1487–1495.

Treating Radionecrosis

- Cox-2 inhibitor
- 100-200 mg po bid
- Renal function
- Sulfa Allergy
- Off-label

Khan et al. J Ped Hem Oncol 2004; 26(4): 253-5

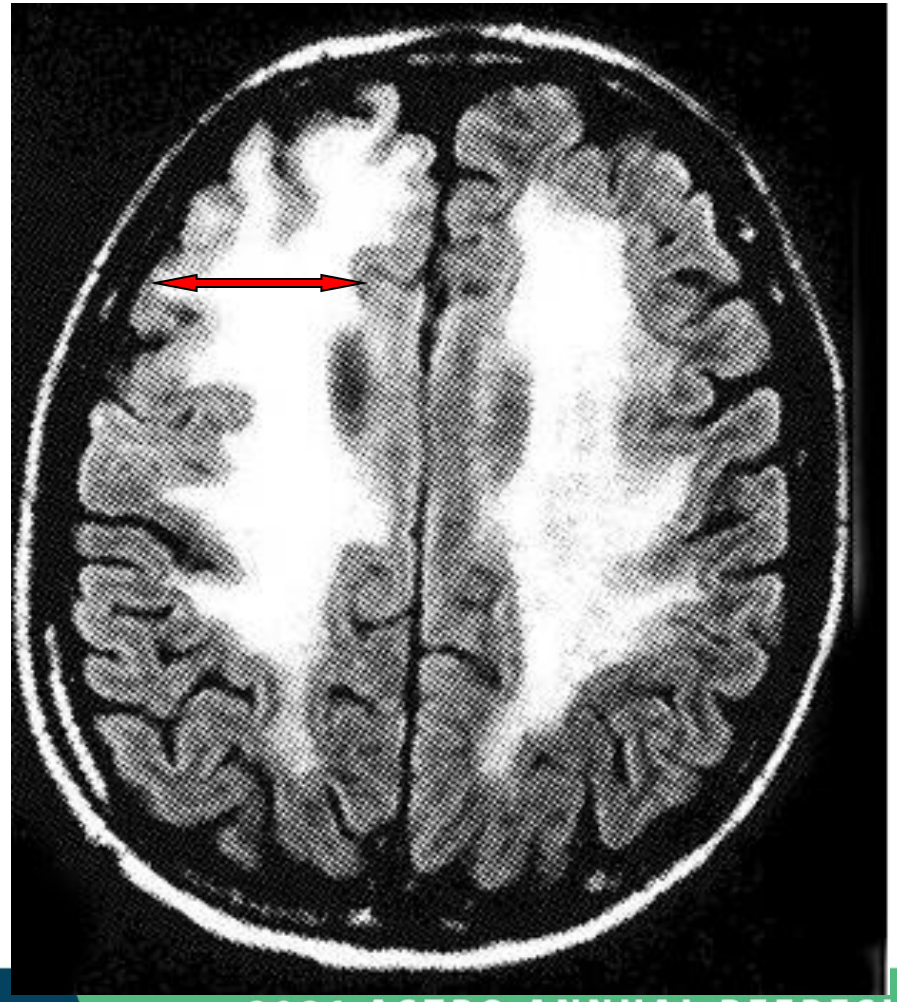
HA-WBRT-NRG CC-001

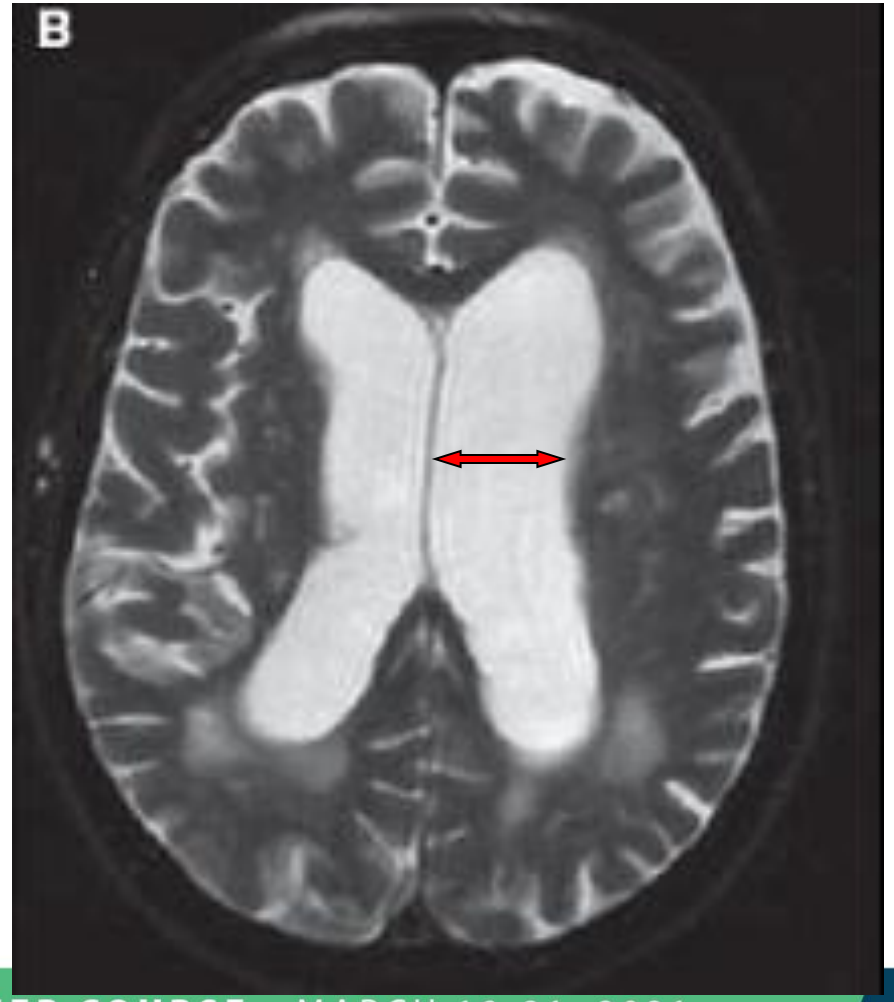
with Memantine

- Phase III Trial of Non-radiosensitive, non LMD
- WBRT + Memantine +/- Hippocampal avoidance
- HR for NCF: 0.74, p=0.02
  - Lower risk for exec function at 4 mos (p=0.01)
  - Lower risk for encoding and consolidation at 6 mos (p=0.02)
  - Pt reported fatigue, speaking, memory improved at 6-mos
- No difference in toxicity, OS, CNS progression

Gondi et al ASCO2019

Normal Pressure Hydrocephalus

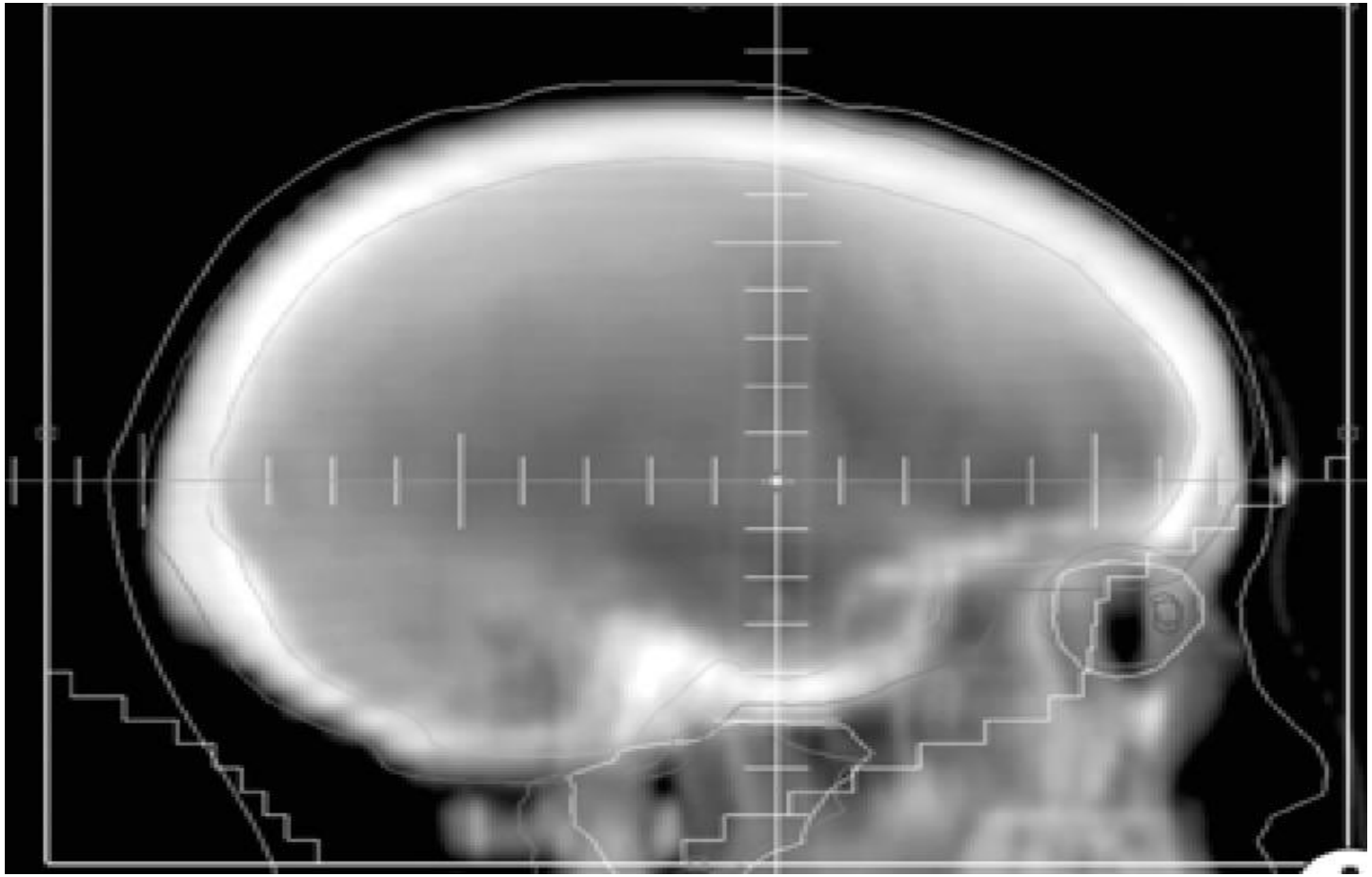




Clinical Pearl

- “Magnetic gait”
- Urinary urgency → incontinence
- Short term memory/multitasking deficit
- Confusion
- Compare pre-RT/post RT third ventricle
- http://www.lifenph.com/

Whole Brain Radiation port



Meningioma

Simpson Surgical Resection Grading

GRADE	DEFINTION	RECURRENCE (%)
0*	GTR tumor, dural attachment, and bone plus stripping of 2 cm-4 cm dura	0% @ 5 years**
1	GTR tumor, dural attachment, abnormal bone	9
2	GTR tumor, coagulation of dural attachment	19%
3	GTR without resection or coagulation of dural attachment; extradural extension (invaded or hyperostotic bone)	29%
4	Partial resection of tumor	44%
5	Decompression +/- Biopsy	-

Simpson, D. 1957. Journal of neurology, neurosurgery, and psychiatry, 20(1), pp.22–39.

Histopathology

- 100% islets distant from index lesion
- 64% macroscopic 1-3 cm away
  - Smaller ones apparent w/ formalin fixing
- 57% microscopic islets
- All cases had distant islets

Borovich, B.1986. Journal of Neurosurgery, 64(1), pp.58–63.
Borovich, B. 1986. JNS, 65(2), pp.168–171.

Karolinska: 25-yr Follow-Up

Late failures dominated by low grade tumors with low proliferative index

Table 2. Number of Patients With a Recurrence After 10 and 25 Years, According to Surgical Radicality

Simpson Grade	10 years	25 years
4-5 (13 p)	62% (8 p)	69% (8+1 p)
3 (12 p)	33% (4 p)	42% (4+1 p)
1-2 (24 p)	13% (3 p)	38% (3+6 p)

p, number of patients.

Pettersson-Segerlind, JWNEU, 76(6), pp.564–571.

Morbidity and Mortality at 25-years

- 42% patients after gross total resection relapse by 25 years
- 33% of patients with gross total rxn die meningioma-related death
- 32% of patients with WHO I at dx died meningioma-related death
- 18/51 patients had 32 re-operations
- 12/18 patients re-op pathology increasingly aggressive

Pettersson-Segerlind, J. WNEU, 76(6), pp.564-571.

Increasingly aggressive with recurrence

Post recurrence PF interval shortened

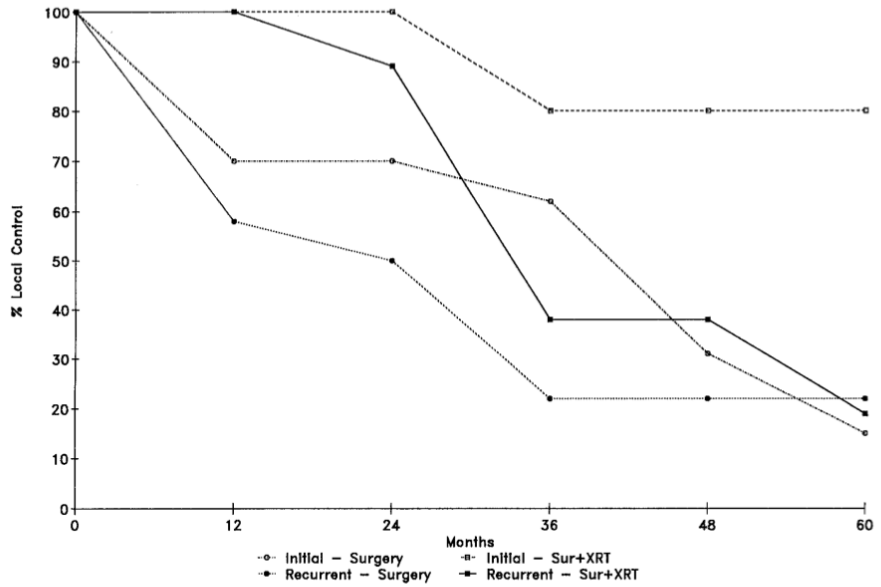


Figure 3. Local control: initial versus recurrent disease, with and without radiotherapy.

Significant on MVA

Table 6. Post surgical median time to recurrence/progression

Median time to recurrence	Surgery alone	Surgery + XRT	Early*	Late*
– Initial presentation	43.5 mo	> 70.0 mo	(p = 0.061)	(p = 0.041)
– Recurrent disease	18.0 mo	34.1 mo	(p = 0.010)	(p = 0.057)
– Combined	27.2 mo	38.9 mo	(p = 0.008)	(p = 0.027)

* Probabilities of early recurrence were calculated using the Wilcoxon 1-tail test, and late recurrences using Log Rank 1-tail test.

Dziuik et al. J Neuro-oncol. 37:177-88. 1998.

Increasingly aggressive with recurrence

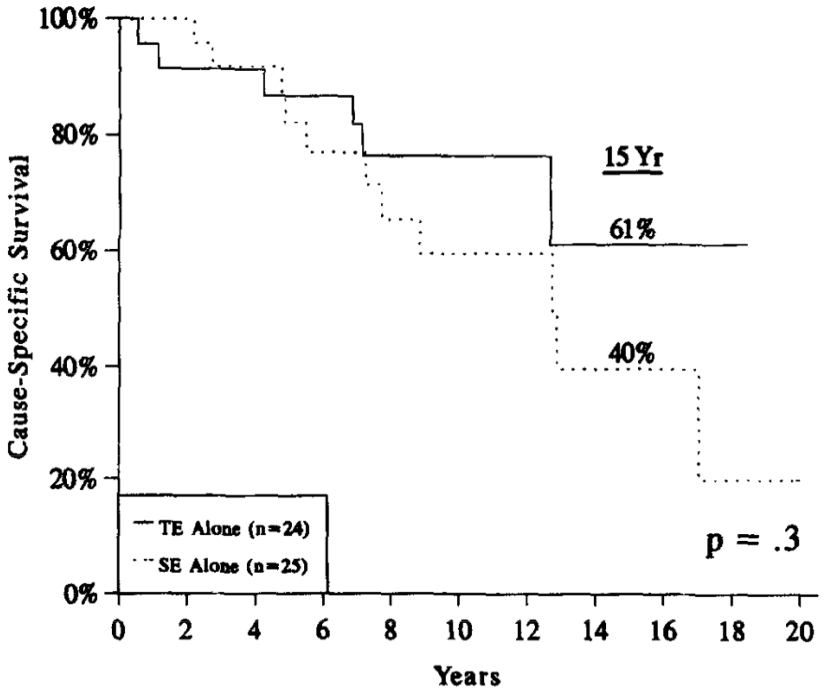


Fig. 6. Cause-specific survival for 49 patients with recurrence after initial treatment with surgery alone according to the extent of initial surgery at the University of Florida. TE Alone, total excision alone; SE Alone, subtotal excision alone.

- *Independent of extent of resection or growth rate,* recurrence portends worse outcome
- 10% incidence *histologic degeneration* after surgery alone

Condra IJROBP 39: (2). P 427-36. 1997

Take Home

- Benign tumors have “skip lesions”
- “Surgical CTV” associated with better long-term control
- 5 (even 10) year follow-up not sufficient to assign “cure”
- Risk of death from even benign meningioma is high
- Recurrence poor prognosis regardless of initial treatment:
- Salvage not as effective as aggressive upfront treatment

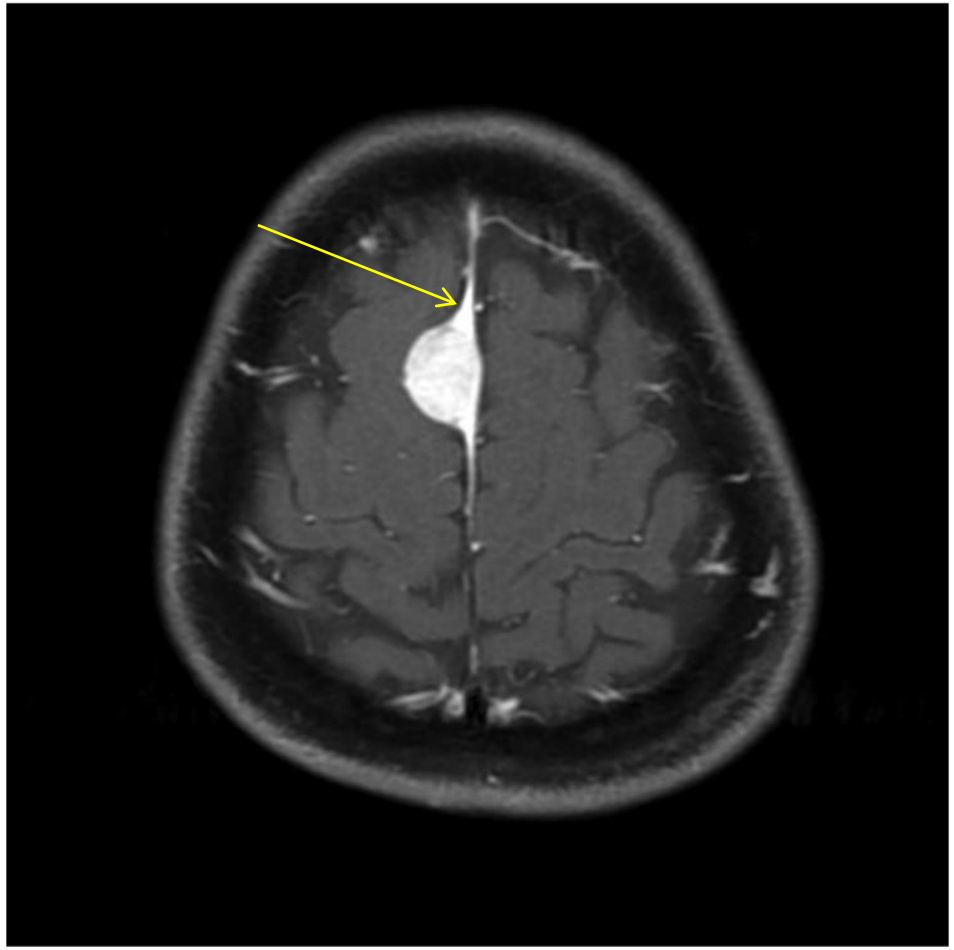
TECHNIQUE

Radiosurgery and Margins

Conformity index (CI)	LC
CI ≥1.4	96.0%
CI <1.4	77.3%

Dibiasi et al. IJROBP. 60(5).1515-19. 2004

Target



- Dural tail is <u>not</u> attachment
- *Attachment* factors in Simpson grading
- Tail: hypervascular dura
- Tumor islets not disproportionately represented in tail

Rogers, L. IJROBP 2004;60:1515

Study	Median F/u (mos)	LC (%)	Overall survival	Cause-specific Survival	Toxicity
Mendenhall. Cancer 98(7) 1473. 2003	60	95	85	97	
Kondziolka Neurosurgery 62:53-60 2008	48	97% 93% Gd1 50% Gd 2 @ 2-yr 15% Gd 3 @ 15 mos		99% @ 2—yrs Gd 1 96% @ 5/10 –yrs Gd1	
Williams Neurosurgery 114:1571-77 2011	84	95% @ 5-yrs 69% @ 10-yrs			10%- CN deficits
Hasegawa J. Neurosurg 107:745-51 2007	62	87% 5-yrs actuarial 73% 10 –yrs actuarial			12%-worsening/new
Kreil JNNP 76:1425-30 2005	95	98.5-5-yr actuarial 97.2% 10-yr actuarial			3.5%-worsening
Pollock IJROBP, 83(5), pp.1414–1418 2012	*63 - Mean +/- 44	99.4 @ 3- and 10-yrs (actuarial)			8.3%-1-yr 11.5%- 5-yrs
Dibiasi IJROBP. 60(5).1515-19. 2004	53	86.2 %-5-yr actuarial 95.2%-CI ≥ 1.4 77.3%CI < 1.4	91%		8.3%

Study	Median F/u (mos)	LC (%)	Overall survival	Cause-specific Survival	Toxicity
Hoe J Korean Neuro Soc 58(4) 379. 2015	48	98%			15% edema 9% symptomatic - 46% Seizure - 43% HA - 21% hemiparesis
Choen-Inbar Neurosurgery 79:58-68 2016.	102	88% 15-yr actuarial 68%			35% Headache 15% CN deficit 16% Dizziness 11% Weakness 4% Encephalopathy 2% Pain 1% Seizure

Symptomatic Edema with Radiosurgery

Parasagittal lesion risk 35%

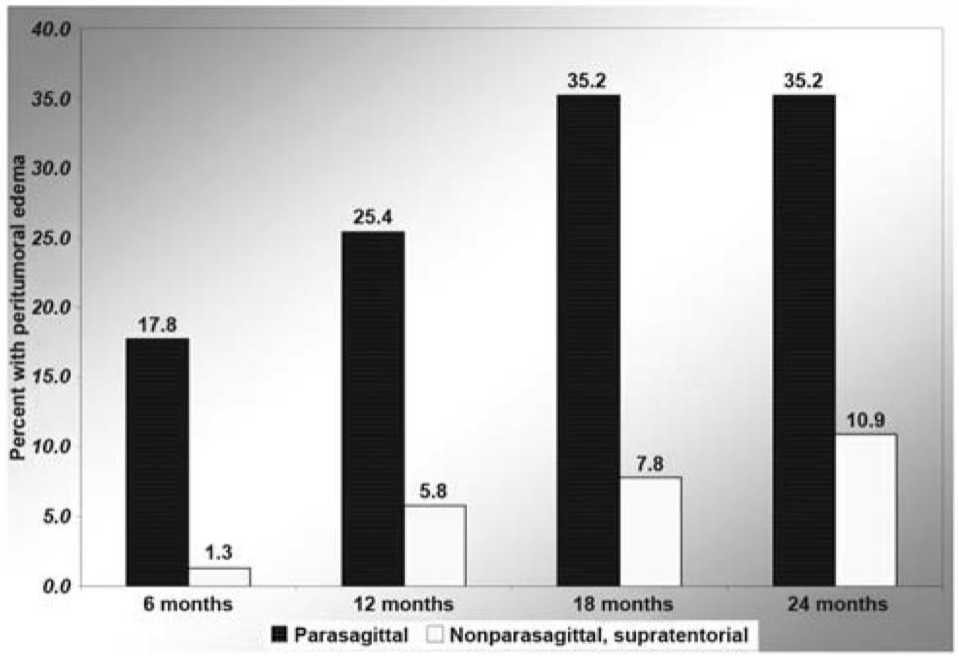


FIGURE 2. *Bar graph showing actuarial rates of development of symptomatic edema after stereotactic radiosurgery of parasagittal and nonparasagittal meningiomas.*

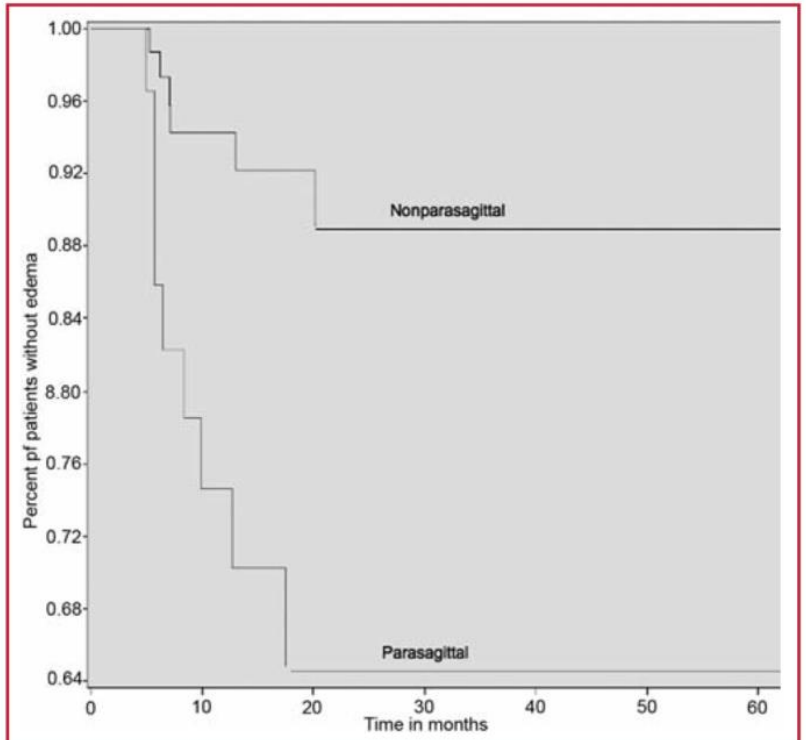


FIGURE 3. *Kaplan-Meier analysis of freedom from symptomatic peritumoral edema after radiosurgery, stratified by meningioma location (parasagittal versus nonparasagittal).*

Patil, 2008. Neurosurgery, 63(3), pp.435–442.

Skull Base SRS Toxicity

GKRS-induced complications	
Intermittent headache	34.8% (n = 47)
Cranial deficit	14.8% (n = 20)
Dizziness	15.6% (n = 21)
Weakness	11.1% (n = 15)
Encephalopathy	3.7% (n = 5)
Pain	1.5% (n = 2)
New or worsening seizures	0.7% (n = 1)
GKRS-induced cranial nerve (CN) deficit	
Trigeminal (CN-V)	10.4% (n = 14)
Vestibulocochlear (CN-VIII)	7.4% (n = 10)
Optic (CN-II)	6.7% (n = 9)
Facial (CN-VII)	5.9% (n = 8)
Hypoglossal	2.2% (n = 3)
Oculomotor (CN-III)	2.2% (n = 3)
Vagus (CN-X)	1.5% (n = 2)
Abducens (CN-VI)	0.7% (n = 1)

Cohen-Inbar, O. 2016. Neurosurgery, 79(1), pp.58–68.

Symptomatic Edema by Technique

Parameter	Group A (SRS) (n = 14)		Group B (FSRT) (n = 16)		*P* value
	n	%	n	%	
SPTE/n	6/14	43	1/16	6	0.031[b]
Surgery necessary SPTE/n	3/14	21	0/16	0	0.089[b]

- 318 patients with meningioma
- Post-tx symptomatic edema
  - SRS:43%
  - SRT: 0%

Radiation therapy modality	
FSRT	253 (79.6)
hFSRT	49 (15.4)
SRS	16 (5.0)

Girvigian 2008. Neurosurgery, 62(5 Suppl), pp.A19–27- A27–8.

Fokas IJROBP 89(3), pp.569–575.

Swedish 25-year Surgical Data

- 42% patients after gross total resection relapse by 25 years
- 33% of patients with gross total rx die meningioma-related death
- 32% of patients with WHO I at dx died meningioma-related death
- 18/51 patients had 32 re-operations
- 12/18 patients re-op pathology increasingly aggressive

Pettersson-Segerlind, J. WNEU, 76(6), pp.564–571.

University of Florida RT Data

- 149 benign meningioma with gross disease
- Median f/u 12-years, all patients updated
- Imaging era (after 1984)
- *All patients at least 10-year non-actuarial follow up*
- Risk of recurrence after DFS
  - 5-yrs: 4%
  - 10-yrs: 3%
  - 15-yrs: 1%

O'steen et al Radiother Oncol. 2019 Aug;137:55-60

University of Florida RT Data

- 5% developed recurrence
- Actuarial rate
  - 10-yrs: 3%
  - 15-yrs: 5%
  - 20-yrs: 8%

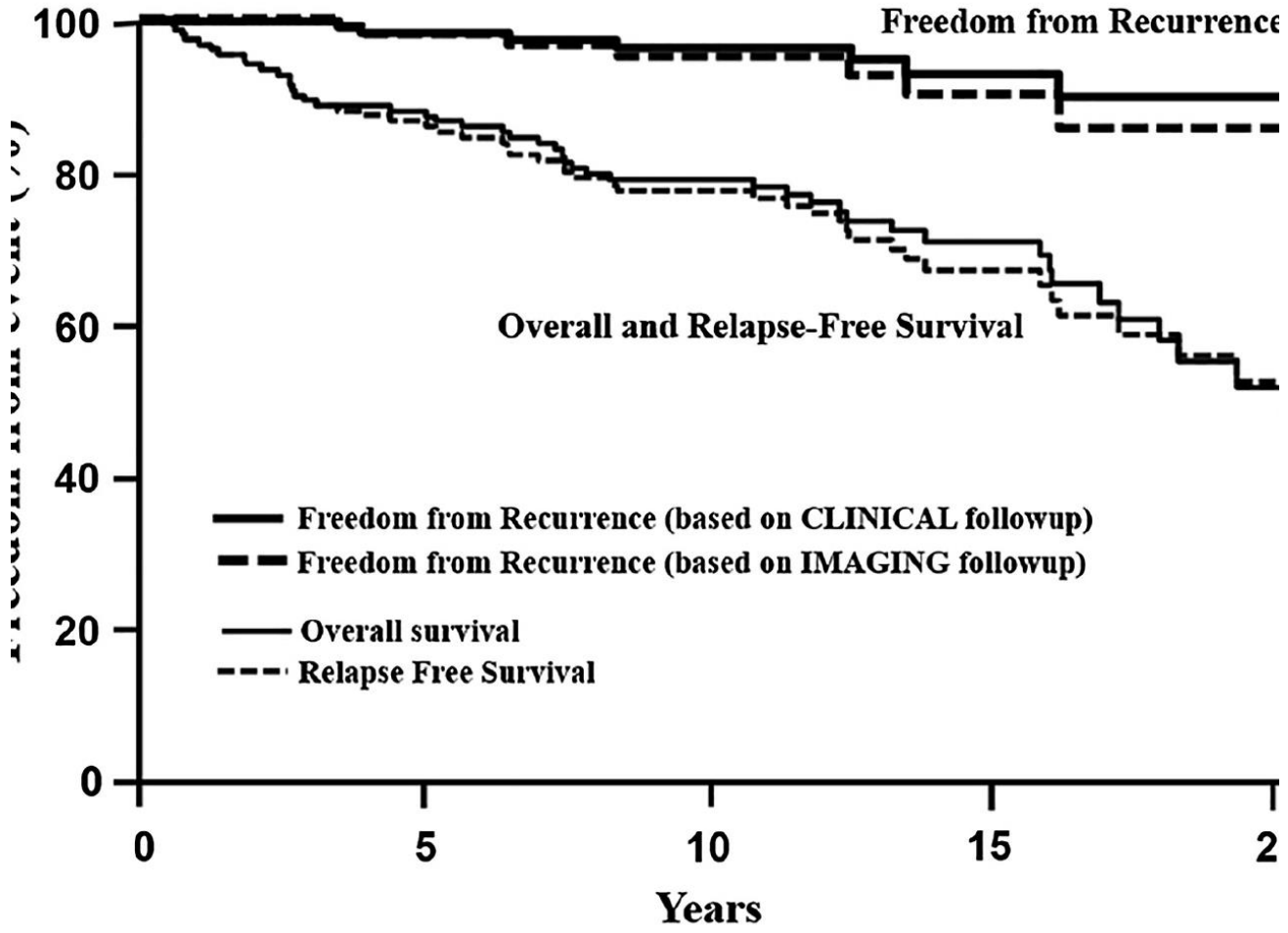
O'steen et al Radiother Oncol. 2019 Aug;137:55-60

RT Freedom From Event

More than half occurrences present > 10-years

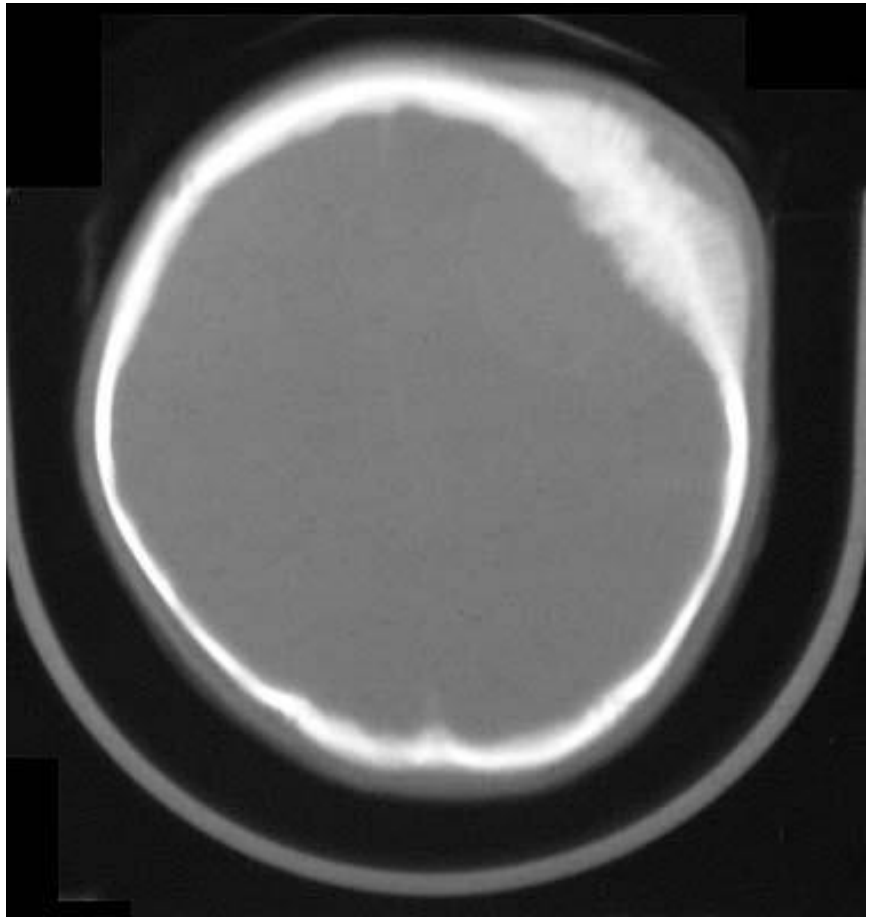
Surgical LR > double at 15 and 20 years

Better than Santacroce SRS database



O'steen et al Radiother Oncol. 2019 Aug;137:55-60

Treatment Planning



Grade I Meningioma

- GTV: Gross lesions
  - CTV: *controversial:*
    - 3 mm margin CTV *along dura*
  - PTV set-up/machine
- Dose: 5400/180 cGy
- Respect normal structures

Grade II Post-Op Planning

- Use both pre- and post-op MRI
- Contour pre-surgical GTV
- Modify pre-surgical GTV on post-op scan to take into account “pushing margins” as normal structures such as brain stem fall back into place post-operatives

Grade II Treatment Planning

- Contour post-operative GTV: gross tumor
- CTV: 5 mm *along dura*
  - Avoiding going into brain parenchyma unless invasion (WHO 2016)
- Consider including involved pre-op dura
  - Particularly if constrained from re-treatment by critical structures
- PTV: Based on system set-up
  - 2-3 mm with SRT/Daily Image guidance.

Grade II Treatment Planning

- Grade II: 5940 cGy
- Cover bone involvement
- Respect normal tissue constraints

Grade III Meningioma

- 2^{nd} cone-down to 64-66 Gy
- Fractions of 2 Gy

RTOG 0539
Intermediate and High Risk Meningioma: RTOG 0539

- GTV: tumor bed and enhancement
  - No edema nor “dural tail”
- CTV60= GTV + 1 cm
- PTV 60= CTV60 plus set up (3-5 mm)
- CTV54= GTV54 + 2cm
- PTV: 54 CTV 54 + set up (3-5 mm)

Conclusion

- Meningioma should be followed longitudinally
- Evidence that a “surgical CTV” exists
- Radiosurgical data still maturing
- Different toxicity profiles with SRS vs. SRT
- Must take multitude of factors into account for patients with potential long-term survival

Conclusion/Summary – at the end of your talk

- What are the main teaching points/takeaways from your talk?
- Include key takeaways after each section of the talk – this allows the audience to digest the material as the talk proceeds.
- What changes do you expect your audience will make as a result of your presentation?
- What improvements in patient care will attendees make as a result of your lecture?
- How does your lecture improve their competency? How does your lecture address barriers to care?
- What key points of your session are “practice changing?” How will the audience incorporate this info into their current practice?

Effective Educational Practices

- Talk titles should inspire curiosity. If you update your talk title, please send it to ASTRO staff so they can update the program.
- Consider making your talk case-based with decision points throughout. Use decision points as opportunities for attendees to take one minute and speak to one another about what they would do. People learn more when they collaborate.
- Spend less time on slides and more time on discussion, questions and answers, and attendee engagement. Be sure you know when your session will be addressing Q&A.